REVIEW

Molecular imaging and radionuclide therapy of pheochromocytoma and paraganglioma in the era of genomic characterization of disease subgroups

David Taïeb^{1,*}, Abhishek Jha^{2,*}, Giorgio Treglia^{3,4,5} and Karel Pacak²

¹Department of Nuclear Medicine, La Timone University Hospital, CERIMED, Aix-Marseille University, Marseille, France

²Section on Medical Neuroendocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA

³Clinic of Nuclear Medicine and PET/CT Center, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

⁴Department of Nuclear Medicine and Molecular Imaging, Lausanne University Hospital, Lausanne, Switzerland

⁵Health Technology Assessment Unit, General Directorate, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

Correspondence should be addressed to K Pacak: karel@mail.nih.gov

*(D Taïeb and A Jha contributed equally to this work)

Abstract

In recent years, advancement in genetics has profoundly helped to gain a more comprehensive molecular, pathogenic, and prognostic picture of pheochromocytomas and paragangliomas (PPGLs). Newly discovered molecular targets, particularly those that target cell membranes or signaling pathways have helped move nuclear medicine in the forefront of PPGL precision medicine. This is mainly based on the introduction and increasing experience of various PET radiopharmaceuticals across PPGL genotypes quickly followed by implementation of novel radiotherapies and revised imaging algorithms. Particularly, ⁶⁸Ga-labeled-SSAs have shown excellent results in the diagnosis and staging of PPGLs and in selecting patients for PRRT as a potential alternative to ¹²³I/¹³¹I-MIBG theranostics. PRRT using ⁹⁰Y/¹⁷⁷Lu-DOTA-SSAs has shown promise for treatment of PPGLs with improvement of clinical symptoms and/or disease control. However, more well-designed prospective studies are required to confirm these findings, in order to fully exploit PRRT's antitumoral properties to obtain the final FDA approval. Such an approval has recently been obtained for high-specific-activity ¹³¹I-MIBG for inoperable/metastatic PPGL. The increasing experience and encouraging preliminary results of these radiotherapeutic approaches in PPGLs now raises an important question of how to further integrate them into PPGL management (e.g. monotherapy or in combination with other systemic therapies), carefully taking into account the PPGLs locations, genotypes, and growth rate. Thus, targeted radionuclide therapy (TRT) should preferably be performed at specialized centers with an experienced interdisciplinary team. Future perspectives include the introduction of dosimetry and biomarkers for therapeutic responses for more individualized treatment plans, α -emitting isotopes, and the combination of TRT with other systemic therapies.

Key Words

- ▶ pheochromocytoma
- ▶ paraganglioma
- ▶ PPGL
- ▶ succinate dehydrogenase complex
- ▶ *SDHB*
- ▶ ¹⁸F-FDOPA
- ▶ ⁶⁸Ga-DOTATATE
- ▶ ¹⁸F-FDG
- ▶ ¹³¹I-MIBG
- ▶ peptide receptor radionuclide therapy
- ▶ theranostics
- ▶ somatostatin receptor

Endocrine-Related Cancer
(2019) 26, R627–R652

Learning points

- 1) Know the molecular taxonomy of pheochromocytoma and/or paraganglioma (PPGL) and the relationship between various genotypes and imaging phenotypes;
- 2) Describe imaging features of *SDHx*-related PPGL;
- 3) Understand pathophysiologic basis of theranostics using iodine-123/131 ($^{123/131}\text{I}$)-metaiodobenzylguanidine ($^{123/131}\text{I}$ -MIBG) and peptide receptor radionuclide therapy (^{177}Lu or ^{90}Y -DOTA somatostatin analogs) and know the results of clinical studies;
- 4) Understand the main areas of improvement of radiotherapeutics in the management of PPGL.

Key messages

- 1) Positron emission tomography imaging using gallium-68 (^{68}Ga)-labeled somatostatin receptor analogs (SSAs) is the most sensitive approach for PPGL localization and can select patients for peptide receptor radionuclide therapy (PRRT).
- 2) Approximately 234 ($n=166$, 71% patients with progressive disease) PPGL patients have been treated on compassionate grounds with PRRT and promising results have been reported mostly in the setting of retrospective small case reports or case series.
- 3) Following a multicentric phase II study, high-specific-activity iodine-131 (^{131}I)-MIBG (Azedra®) has received FDA approval for metastatic or locally aggressive PPGL.
- 4) Potential indications of radiotherapeutics in PPGL include inoperable PPGL with progressive and/or symptomatic metastatic PPGL.
- 5) The future perspectives include the introduction of dosimetry and biomarkers for therapeutic responses for more individualized treatment plans, α -emitting isotopes, and combination of targeted radionuclide therapy with other forms of treatment, including immunotherapy.

Current classification of PPGL

Pheochromocytomas (PHEOs) and paragangliomas (PGLs), together called PPGLs) are neuroendocrine tumors (NETs) arising from neural crest-derived adrenal or extra-adrenal paraganglia, respectively. Around 5–10% of solitary pheochromocytomas are hereditary, whereas tumor multiplicity or extra-adrenal tumors are related to currently known germline mutations in 40–70% of patients.

These are now recognized to be caused by at least 20 susceptibility genes (Dahia 2014, Crona *et al.* 2017, Fishbein *et al.* 2017, Jochmanova & Pacak 2018). A majority of PPGLs can be described as carrying either germline or somatic mutations. Depending on their transcription profile, recent data obtained from The Cancer Genome Atlas (TCGA) has divided PPGL into three clinically relevant clusters:

1. **Pseudohypoxia** group (cluster 1) is divided into at least two subgroups: the first, tricarboxylic acid (TCA) cycle-related germline mutations mainly in succinate dehydrogenase subunits (*SDHx*) and fumarate hydratase (*FH*). The second subgroup includes von Hippel–Lindau tumor suppressor (*VHL*)- and endothelial PAS domain protein 1 (*EPAS1*)-related somatic and germline mutations.
2. **Kinase signaling** group (cluster 2) consists of germline or somatic mutations in ret proto-oncogene (*RET*), neurofibromin 1 (*NF1*), transmembrane protein 127 (*TMEM127*), MYC-associated factor X (*MAX*), and HRas proto-oncogene (*HRAS*).
3. **Wnt signaling** group (cluster 3) includes newly recognized somatic mutations in cold shock domain containing E1 (*CSDE1*), as well as somatic gene fusions affecting mastermind-like transcriptional coactivator 3 (*MAML3*).

Most importantly from a clinical standpoint, some correlations exist between the gene(s) involved and tumor's anatomic location:

- a) PHEO: *RET*, *VHL*, *SDHx*, *NF1*, *MAX*, *TMEM127*, *HRAS*.
- b) Extra-adrenal retroperitoneal PGLs: *SDHx*, *FH*, *VHL* (rare), prolyl hydroxylase 1 and 2 (*PHD1/2*) and *EPAS1*/hypoxia-inducible factor 2 alpha (*HIF2A*).
- c) Head and neck PGL (HNPPGL): *SDHx*.

Major predictors for hereditary PPGL include a family and personal history of PPGL, inherited in an autosomal dominant manner but with varying penetrance, characteristic syndromic presentation, young age at diagnosis, multifocality, unusual location/s (e.g. heart, urinary bladder), and/or tumor recurrence, particularly in the adrenal gland (Neumann *et al.* 2009, 2018, Welander *et al.* 2011, Jafri *et al.* 2013, Benn *et al.* 2015, Favier *et al.* 2015). Renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST), pituitary adenoma, and rarely, pulmonary chondroma, neuroblastoma, and neuroendocrine neoplasms (usually carcinoid) can also be related to *SDHx* and rarely to other PPGL susceptibility gene mutations (Pasini *et al.* 2008, Papathomas *et al.* 2014,

Casey *et al.* 2017). Other clinical manifestations can also be suggestive of particular gene mutations. For example, prior medullary thyroid cancer (MTC) for *RET*, café-au-lait spots/neurofibromas for *NF1*, RCC/hemangioblastomas/pancreatic tumors for *VHL*, congenital polycythemia and duodenal somatostatinoma for *EPAS1/HIF2A* (Zhuang *et al.* 2012), and RCC/leiomyomas for *FH* (Castro-Vega *et al.* 2014).

Furthermore, PPGL with an underlying *SDHB* mutation are associated with a higher risk of aggressive behavior than other hereditary PPGLs leading ultimately to death, particularly due to development of metastatic disease. The risk of metastasis in *SDHB*-related tumors has been estimated to range from 30 to 80% (Gimenez-Roqueplo *et al.* 2003, Neumann *et al.* 2004, Amar *et al.* 2005, 2007, Benn *et al.* 2006, Brouwers *et al.* 2006, King *et al.* 2011, Turkova *et al.* 2016, Hamidi *et al.* 2017). In addition to impacting the distribution of disease, the genomically distinct subgroups of PPGLs have different patterns of catecholamine secretion and the expression of cell membrane receptors and transporters, which impact their imaging phenotype, particularly the uptake of catecholamines or their precursors (Eisenhofer *et al.* 1999, 2011, Fonte *et al.* 2012).

⁶⁸Ga-DOTA-SSAs in PPGL and imaging phenotypes across PPGL subgroups

There are diverse radionuclide imaging techniques available for the diagnosis, staging and follow-up of PPGLs. Beyond their ability to specifically detect and localize PPGLs, these imaging approaches variably characterize these tumors at cellular and molecular levels. More recently, gallium-68 (⁶⁸Ga)-labeled somatostatin receptor analogs (SSAs) positron emission tomography-computed tomography (PET/CT) is being increasingly performed to detect PPGLs and assess their somatostatin receptor (SSTR) expression which is paramount for PRRT in inoperable or locally aggressive/metastatic disease (Nolting *et al.* 2019, Taïeb *et al.* 2019).

In a recent systematic review and meta-analysis, the pooled PPGL detection rate of ⁶⁸Ga-DOTA-SSA PET/CT in patients with unknown genetic status was 93% (95% confidence interval (CI) 91–95%), which was significantly higher than that of ¹⁸F-fluorodihydroxyphenylalanine (¹⁸F-FDOPA) PET/CT (80% (95% CI 69–88%)), ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET/CT (74% (95% CI 46–91%)), and ^{123/131}I-MIBG scintigraphy (38% (95% CI 20–59%), *P* < 0.001 for all) (Han *et al.* 2019).

This meta-analysis demonstrated the intrinsic value of ⁶⁸Ga-DOTA-SSA PET/CT in the detection of PPGL even when a physician is not aided by the knowledge of genetic status of the patient. On the contrary, in another meta-analysis (Kan *et al.* 2018), ⁶⁸Ga-DOTA-SSA PET/CT detected more PPGL lesions with germline mutations (did not specify the exact mutation) than ¹⁸F-FDG PET/CT (97 vs 79%); however, only four studies (pooled patients = 79) included in this meta-analysis used both radiopharmaceuticals (Janssen *et al.* 2015, 2016a, Tan *et al.* 2015, Chang *et al.* 2016).

In a recent non-comparative study from the Royal North Shore Hospital in Australia, ⁶⁸Ga-DOTATATE PET/CT was evaluated for initial staging (*n* = 28) and restaging (*n* = 18, including eight metastatic cases) for PHEOs and for initial staging (*n* = 8) and restaging (*n* = 18, including four metastatic cases) for PGLs. Overall, ⁶⁸Ga-DOTATATE PET/CT had a sensitivity of 84% for PHEO (21/24) and 100% (7/7) for PGL (Gild *et al.* 2018). Further, ⁶⁸Ga-DOTATATE PET/CT resulted in change of management in 50% PHEOs (23/46) and 44% (12/27) PGLs.

In a retrospective mixed cohort study in 12 patients of neural crest tumors (*n* = 11, PPGL; *n* = 1, medullary thyroid carcinoma), per patient and per lesion detection rates of ⁶⁸Ga-DOTATATE PET/CT was found to be superior to ¹²³I-MIBG SPECT/CT (83% (10/12) vs and not vs 42% (5/12) and 96.7% (29/30) vs and not vs 23.3% (7/30)), respectively (Naji *et al.* 2011). Further, three of four *SDHB* patients were detected by ⁶⁸Ga-DOTATATE PET/CT, whereas ¹²³I-MIBG SPECT/CT was negative in all *SDHB* patients (Naji *et al.* 2011). ⁶⁸Ga-DOTATATE performed superior to ¹⁸F-FDG PET/CT (96.2 vs 91.4%) in a mixed cohort of 23 (*n* = 10 *SDHx* mutated) patients and ^{123/124}I-MIBG detected very few lesions (30.4% in 7 patients) (Chang *et al.* 2016). Also, per lesion detection rate of ⁶⁸Ga-DOTATATE PET/CT was superior to ¹²³I-MIBG scintigraphy (100%, 29/27 vs and not vs 6.9%, 2/27) in ten extra-adrenal PGL patients (Kroiss *et al.* 2015).

The use of ⁶⁸Ga-DOTA-SSA has shown excellent results in localizing PHEOs or PGLs, including primary and/or metastatic PPGLs (Naji *et al.* 2011, Sharma *et al.* 2013, 2014, 2015, Hofman *et al.* 2015, Kroiss *et al.* 2015).

Head-to-head comparison between ⁶⁸Ga-DOTA-SSAs and ¹⁸F-FDOPA PET/CT has been performed in only seven studies: one retrospective study from Innsbruck Medical University (⁶⁸Ga-DOTATOC in 20 patients with unknown genetic background) (Kroiss *et al.* 2013), five prospective studies from the National Institutes of Health (NIH) (⁶⁸Ga-DOTATATE in 17 patients with metastatic *SDHB*–, 22 patients with metastatic sporadic,

20 patients with HNPGLs, 14 patients with polycythemia and PGL syndromes, and 23 patients with *SDHD*-related PPGL, respectively) (Janssen *et al.* 2015, 2016a,b, 2017, Jha *et al.* 2018a) and one prospective study from La Timone University Hospital (^{68}Ga -DOTATATE in 30 patients) (Archier *et al.* 2016) (Table 1). The separate data for apparently sporadic PHEO could be extracted from one study (Archier *et al.* 2016) for ten patients in whom ^{18}F -FDOPA PET/CT showed better patient-based and lesion-based detection rates than ^{68}Ga -DOTA-SSA PET/CT (100 vs 90% and 94 vs 81%, respectively). ^{68}Ga -DOTA-SSA PET/CT might be inferior to ^{18}F -FDOPA PET/CT in the detection of small PHEOs (Archier *et al.* 2016). However, the preliminary study from NIH in apparently sporadic PHEOs shows that ^{68}Ga -DOTA-SSA performs similar to ^{18}F -FDOPA PET/CT (Jha *et al.* 2019b).

The elevated clinical value of ^{68}Ga -DOTATATE was also observed in the pediatric population with *SDHx* mutation (Jha *et al.* 2018b). ^{68}Ga -DOTA-SSA PET/CT can therefore, be recommended for diagnosis, staging, and follow-up imaging of PPGL with underlying *SDHx* mutations (Janssen *et al.* 2015, Jha *et al.* 2018a,b, 2019a). Further, it is suggestive that ^{68}Ga -DOTA-SSA PET/CT is the most sensitive tool in the detection of HNPGLs, especially *SDHD*-related tumors, which may be very small in size and/or fail to sufficiently concentrate ^{18}F -FDOPA (Fig. 1). One would consider that detection of additional sites in patients with diffuse metastatic disease is of limited interest. However, many of these lesions are not well characterized (small nodes) or even detected (bone marrow metastases) by anatomical imaging. The suboptimal value of conventional imaging poses a diagnostic challenge in the evaluation of metastatic PPGL patients. Although assessment of RECIST criteria by cross-sectional imaging is currently the referential method, incorporation of PET using SSA as part of a surveillance program seems prudent for accurate evaluation (Kong *et al.* 2019). Also, functional imaging can localize subcentimetric new lesions which take time to appear on cross-sectional imaging, and hence, can aid in change of treatment earlier in case of progression. Further, in biochemically negative patients, the tumor load can be adequately determined by the functional imaging.

Follow-up imaging varies from patient to patient. The more intensive follow-up imaging is required in metastatic patients or patients who are at high risk to develop metastases. Such high risk-factors have been identified as *SDHB*, *SDHA* germline mutations, *ATRX* mutation, male sex, patient with large primary tumors (various studies have identified that from >4.5–5 cm to

>10 cm), noradrenergic or dopaminergic biochemical phenotype, older age at primary tumor diagnosis (>40–50 years), and high proliferative index (Ayala-Ramirez *et al.* 2011, King *et al.* 2011, Schovaneck *et al.* 2014, Plouin *et al.* 2016, Hamidi *et al.* 2017, Jha *et al.* 2019a, Crona *et al.* 2019, Hescot *et al.* 2019, Mei *et al.* 2019). These patients should be followed up indefinitely involving either whole-body CT/MRI and/or functional imaging. All of these patients should receive whole-body CT/MRI at baseline along with whole-body functional PET/CT imaging per algorithm for the staging. Depending upon the severity of disease and therapy (chemotherapy, cold SSA, PRRT), the optimal length of follow-up imaging in these patients should be decided. The patients with high metastatic load (lungs and liver metastases) and/or progressive disease should be imaged every 6–8 months, whereas the metastatic patients who are stable or are under wait-and-watch protocol should be imaged every 12 months. At our institution, every patient gets whole-body anatomic and functional follow-up imaging. The information from anatomic and functional imaging along with biochemical results and clinical information is considered during evaluation regarding disease progression. The patients with only primary tumors, follow-up anatomic imaging should occur after 3 months of surgical resection to evaluate residual and/or recurrent tumor. Following no evidence of recurrence/residual disease, repeat follow-up imaging should take every year for first 5 years and then if the patient is free of disease, it can be increased to every 3 years; however, patients should receive yearly biochemical evaluation. The response evaluation using RECIST, PERCIST, and EORTC has been described in solid tumors. However, they have not been validated in PPGL especially PERCIST or EORTC using ^{68}Ga -DOTA-SSA PET/CT. Further studies in this regard would be warranted. Moreover, metabolic tissue burden can have a significant effect on SUV measurements for PET imaging. So, when using PET response, this effect should be mitigated by normalizing uptake values to a reference tissue (blood pool or liver) (Viglianti *et al.* 2018). Further, when ^{68}Ga -DOTA-SSA PET/CT is used to evaluate long-acting SSA therapy, it must be kept in mind that in most cases long-acting SSA therapy increases intensity of uptake (both SUVmax and normalized to liver) within metastases, and hence, the results should be interpreted accordingly (Cherk *et al.* 2018).

The rare mutations *EPAS1* (*HIF2A*), *PHDs*, *MAX*, and *FH* remain an exception among susceptibility genes since they lead to PPGLs that concentrate less

Table 1 Per lesion and per patient detection rates of 68Ga-DOTA-SSA PET/CT with 18F-FDOPA PET/CT and/or 18F-FDG PET/CT and/or anatomic imaging in various cohorts of PPGL.

Cohort	Authors/ Year	Country	Type of study	Gold Standard	No. of PPGL patients (n)	68Ga-DOTA-SSA		18F-FDOPA		18F-FDG		CT/MRI	
						Per patient	Per lesion	Per patient	Per lesion	Per patient	Per lesion	Per patient	Per lesion
Metastatic SDHB-related PPGL	Janssen <i>et al.</i> 2015	USA	Prospective single center	Composite of anatomic and functional imaging	17	17/17 (100%) n = 17	285/289 (98.6%) n = 17	14/16 (87.5%) n = 17	175/285 (61.4%) n = 16	17/17 (100%) n = 17	248/289 (85.8%) n = 17	17/17 (100%) n = 17	245/289 (84.8%) n = 17
Sporadic metastatic PPGL	Janssen <i>et al.</i> 2016a	USA	Prospective single center	Composite of anatomic and functional imaging	22	22/22 (100%) n = 22	450/461 (97.6%) n = 22	11/12 (91.7%) n = 12	181/242 (74.8%) n = 12	20/22 (90.9%) n = 22	226/461 (49.2%) n = 22	22/22 (100%) n = 22	376/461 (81.6%) n = 22
Pediatric SDHx-related PPGL	Jha <i>et al.</i> 2018b	USA	Retrospective single center	Composite of anatomic and functional imaging	9	8/8 (100%) n = 8	100/107 (93.5%) n = 8	N.A.	N.A.	8/8 (100%) n = 8	85/107 (79.4%) n = 8	8/8 (100%) n = 8	79/107 (73.8%) n = 8
Head and neck PGL	Janssen <i>et al.</i> 2016b	USA	Prospective single center	18F-FDOPA or CT/MRI	20	N.A.	38/38 (100%) n = 20	N.A.	37/38 (97.4%) n = 20	N.A.	27/38 (71.1%) n = 20	N.A.	23/38 (60.5%) n = 20
Polycthemia- PGL syndrome	Janssen <i>et al.</i> 2017	USA	Prospective single center	Composite of anatomic and functional imaging	14	N.A.	24/68 (35.3%) n = 13	N.A.	73/74 (98.7%) n = 14	N.A.	22/52 (42.3%) n = 13	N.A.	44/74 (60.3%) n = 14
MAX-related PPGL	Taieb <i>et al.</i> 2018	USA, France	Retrospective bicentric	Histology	6	3/3 (100%) n = 3	4/7 (57.1%) n = 3	6/6 (100%) n = 6	20/22 (90.9%) n = 6	2/4 (50.0%) n = 4	2/11 (18.2%) n = 4	5/6 (85.7%) n = 6	11/21 (52.4%) n = 6
Mixed cohort	Archier <i>et al.</i> 2016	France	Prospective single center	Histology and composite of anatomic and functional imaging	30	28/30 (93%) n = 30	43/46 (93%) n = 29	29/30 (97%) n = 30	41/46 (89%) n = 29	N.A.	N.A.	28/30 (93%) n = 30	35/46 (76%) n = 29
Extraadrenal PGL	Kroiss <i>et al.</i> 2013	Austria	Retrospective single center	Combined cross- sectional imaging	20	20/20 (100%) n = 20	45/45 (100%) n = 20	20/20 (100%) n = 20	32/45 (71.1%) n = 20	N.A.	N.A.	N.A.	N.A.

Includes the studies where head-to-head comparison between 68Ga-DOTA-SSA PET/CT and 18F-FDOPA PET/CT was performed. The data from 18F-FDG PET/CT and/or anatomic imaging was also included if they were available. The reference standard or denominator was heterogeneous among various studies and ranged from histology to composite of anatomical and functional imaging. Even though pathology is considered as gold standard, in patients with metastatic disease biopsy of multiple sites is neither feasible nor ethical. Therefore, adoption of a composite of imaging and/or pathologic findings should be considered a robust alternative (Hofman & Hicks 2015).

Figure 1

Multifocal *SDHD*-related vagal PGLs (VPGLs). (A) Craniocervical ^{18}F -FDOPA PET image (maximum intensity projection: MIP) showing the two VPGLs (arrows). (B) Craniocervical ^{68}Ga -DOTATATE image (MIP) showing two VPs (arrows) with higher tumor uptake compared to ^{18}F -FDOPA PET. (C, D, E) Magnetic resonance (MR) images (C) T2-weighted image; (D) T1-weighted dynamic contrast enhanced (DCE) image; (E) T1-weighted DCE image/T2 weighted image fusion image) showing both VPGLs with arterial enhancement pattern on magnetic resonance angiogram images.

^{68}Ga -DOTA-SSA in contrast to *SDHx*-related and other PPGLs; however, findings need to be confirmed in a larger group of patients with *FH* mutation (Darr *et al.* 2016, Nambuba *et al.* 2016, Janssen *et al.* 2017, Taïeb *et al.* 2018). The mechanism for this phenotype is currently largely unexplained. Von Hippel-Lindau syndrome, which is another pseudohypoxia-related disorder but with normal succinate levels, presents with a high ^{18}F -FDOPA uptake in contrast to ^{18}F -FDG uptake that varies from low to high. In the kinase signaling group, ^{18}F -FDOPA is probably the best radiopharmaceutical

due to its high tumor uptake together with a limited uptake in the remaining (unaffected) adrenal gland (Taïeb *et al.* 2018). However, data are still limited regarding the value of ^{68}Ga -DOTA-SSA PET/CT in these patients including MEN2 syndrome patients where head-to-head comparison with ^{18}F -FDOPA has to be performed to provide any firm clinical conclusion and recommendation (Figs 2 and 3). However, for MEN2 patients with positive biochemistry and CT/MRI showing unilateral or bilateral adrenal tumors, functional imaging is not needed.

Figure 2

Proposed clinical algorithm for nuclear imaging investigations of pheochromocytoma/paraganglioma patients according to genotype. The algorithm has been proposed for patients with suspected or confirmed PPGL in order to help toward the appropriate use of PET radiopharmaceuticals across PPGL subtypes. It may suffer from potential limitation of reported small number of cases. The optimal follow-up algorithm for non-proband *SDHx*-associated PPGLs remains to be determined but mostly relies on annual biochemical screening and CT/MRI at regular intervals.

Figure 3
First-choice PET radiopharmaceuticals across
genotypes.

As proposed in Fig. 2, when genetic status is unknown and in the absence of tumor multifocality or familial trait, ^{68}Ga -DOTA-SSA PET/CT should be proposed as first-line imaging modality in HNPGL, sporadic PHEO, extra-adrenal PGL, and metastatic cases (Kroiss *et al.* 2013, Janssen *et al.* 2016a,b, Jha *et al.* 2018a,b, 2019a,b, Han *et al.* 2019). For those associated with mutations in *NF1/RET/MAX*, ^{18}F -FDOPA PET/CT should be recommended first due to the optimal tumor-to-adrenal uptake ratio that facilitates their detection. However, since ^{18}F -FDOPA is not widely available, this could be replaced by ^{68}Ga -DOTA-SSA or ^{123}I -MIBG depending upon specific technical or legislative limitations across countries. ^{123}I -MIBG is also needed to select potential patients with ^{131}I -MIBG therapy (Fig. 2). Many of these reports are based on extremely rare cohorts (*HIF2A*, *PHD1/2*, *FH*, *MAX*, pediatric *SDHx*); therefore, these studies have extremely small number of patients. However, due to the lack of information on functional imaging modalities available in the scientific literature, it becomes important to report findings obtained from even small study cohort. Also, the reference standard or

denominator was heterogeneous among various studies and ranged from histology to composite of anatomical and functional imaging. Even though pathology is considered as gold standard, in patients with metastatic disease, biopsy of multiple sites is neither feasible nor ethical. Therefore, adoption of a composite of imaging and/or pathologic findings should be considered a robust alternative (Hofman & Hicks 2015).

More recently, new radiopharmaceuticals have been proposed (^{124}I -MIBG, ^{18}F -MFBG) for targeting norepinephrine transporter and appear superior to ^{123}I -MIBG (Hartung-Knemeyer *et al.* 2012, Cistaro *et al.* 2015, Pandit-Taskar *et al.* 2018).

Theranostics

Personalized (precision) medicine has already made its mark and has the potential to enhance patient management. It consists in adapting healthcare strategies tailored to individual and disease characteristics.

Beyond the expected clinical benefits of personalized medicine, theranostics could also have a significant positive economic effect (Taïeb *et al.* 2016). Nuclear medicine has a central role in personalized medicine via theranostic approaches. The term 'theranostics' was coined by John Funkhouser which encapsulates the integration of *diagnostic* and *therapeutic* functions within the *same pharmaceutical platform (a theranostics pair)* (Kelkar & Reineke 2011). Therefore, results derived from an imaging study based on a compound labeled with a diagnostic radionuclide can precisely determine whether an individual patient is likely to benefit from a specific treatment using the same related compound labeled with a therapeutic radionuclide. Initially, $^{123/131}\text{I}$ -MIBG targeting norepinephrine transporter system and more recently $^{68}\text{Ga}/^{90}\text{Y}/^{177}\text{Lu}$ -DOTA-SSA analogs targeting peptide (somatostatin) receptors have been introduced as theranostic agents for PPGLs (Nolting *et al.* 2019).

^{131}I -MIBG theranostics

In advanced PPGLs, ^{131}I -MIBG treatment is still recommended for ^{123}I -MIBG-positive patients. Conventional ^{123}I -MIBG scintigraphy is first used to assess these tumors for the presence of cell membrane norepinephrine transporter system. However, the majority of studies on ^{131}I -MIBG theranostics are retrospective, heterogeneous in terms of baseline patient characteristics, and use of treatment protocols. A large systematic review and meta-analysis of 17 studies comprising 243 patients on ^{131}I -MIBG published between 1984 and 2012 (follow-up duration, 24–62 months) showed a complete response, partial response, and stable disease in 3% (95% CI, 6–15%), 27% (95% CI, 19–37%), and 52% (95% CI, 41–62%) of pooled patients, respectively (van Hulsteijn *et al.* 2014).

One of the main drawbacks of conventional MIBG preparations is that more than 99% of the MIBG molecules are not labeled with ^{131}I , therefore, possibly competing for norepinephrine transporter-binding sites and disrupting norepinephrine reuptake mechanism. This may lead to decreased absorbed dose and possibly increased side effects especially with high-dose administrations (>12 mCi/kg) (Gonias *et al.* 2009, Carrasquillo *et al.* 2016). Hematotoxicity was the most significant toxicity especially thrombocytopenia (Carrasquillo *et al.* 2016). Low-dose administrations (149 mCi) were well tolerated; however, following high-dose administrations (>12 mCi/kg), grade 3 or 4 thrombocytopenia and leukopenia was observed

in 83–87% of patients, requiring platelet transfusion and growth factors (>12 mCi/kg) (Gonias *et al.* 2009, Carrasquillo *et al.* 2016). Myelodysplastic syndrome (MDS) and acute leukemias (ALs) have been reported in patients treated with large amounts of ^{131}I -MIBG and chemotherapy (Carrasquillo *et al.* 2016) with a 4% of MDS incidence with high-dose administrations (Gonias *et al.* 2009). Other reported toxicities are hypothyroidism (11–20%) even with low-dose administrations, hypogonadism with both low-dose and high-dose administrations, acute respiratory distress syndrome and bronchiolitis obliterans and hypertension with high-dose administrations only (Carrasquillo *et al.* 2016). Hypertensive crises (despite blocking reuptake of norepinephrine), renal failure, and hepatotoxicity were rarely reported (Carrasquillo *et al.* 2016). More recently, high-specific-activity (HSA) ^{131}I -MIBG that consists almost entirely of ^{131}I -MIBG (HSA, ~2500 mCi/mg, 92,500 MBq/mg) has been developed (Pryma *et al.* 2019). In a recent multicentric phase II study by Pryma *et al.*, 68 and 50 PPGL patients received one or two therapeutic doses of HSA ^{131}I -MIBG, respectively (Pryma *et al.* 2019). All treated patients had disease progression on prior therapy or were ineligible for chemotherapy or other therapies. HSA ^{131}I -MIBG was administered at 0.3 GBq/kg. Of the 68 patients who received at least one therapeutic dose of HSA ^{131}I -MIBG, 17 (25%; 95% CI, 16–37%) had a durable reduction in baseline antihypertensive medication use. Most patients (92% among the 64 patients) with evaluable disease experienced partial response (23.4%, 15/64) or stable disease (68.7%, 44/64). The median overall survival (OS) was 37 months (95% CI, 31–49 months); however, it was 44 months (95% CI, 32–60 months) for patients who received two therapeutic doses of HSA ^{131}I -MIBG versus 18 months (95% CI, 4–31 months) for those who received one dose. Prolonged myelosuppression was the most common cause for patients not receiving the second therapeutic dose. Interestingly, median survival rates for patients with or without lung and/or liver metastases was similar (43 vs 41 months). No patients had drug-related acute hypertensive events. Sixty-one patients (90%) experienced hematologic adverse events, which were grade 3 or 4 adverse events or other severe adverse events in 49 (72%) of these patients. Seventeen patients (25%) required hematological supportive care. Treatment-related serious adverse events included hematologic toxicities (13 patients, 19%), pulmonary embolism in two patients (3%), MDS in three patients (4%). Secondary malignancies included acute myeloid leukemia and acute lymphocytic leukemia in one patient each.

HSA ^{131}I -MIBG has recently received FDA approval. Although effective, the use of HSA ^{131}I -MIBG is associated with higher rate of hematologic toxicity which possibly got amplified due to previous cytotoxic therapies together with some individual susceptibilities. However, these side effects should be well considered before recommending it to patients and they need to be informed about the risks when being consented for such a therapeutic option. ^{123}I -MIBG scintigraphy should be used as a theranostic radiopharmaceutical for determining if a patient is eligible for ^{131}I -MIBG therapy and patient-specific dosimetry should be performed to optimize therapy. Although not widely available, the PET equivalent, ^{124}I -MIBG, has significant advantages in terms of spatial resolution and its ability to quantify uptake for more reliable dosimetry calculations that would be preferable when HSA ^{131}I -MIBG is considered as a therapeutic option.

PRRT using radiolabeled-somatostatin analogs

PPRT in NET (PPGL excluded)

PRRT is now a well-established treatment option for well-differentiated advanced NETs. The principle of SSTR-directed PRRT is to selectively deliver radiation dose to tumors that overexpress SSTRs with preservation of healthy surrounding tissues. PRRT is based on the administration of SSA labeled with a therapeutic isotope (e.g. ^{177}Lu (^{177}Lu), ^{90}Y (^{90}Y)). Selection of good candidates is based on the use of a companion diagnostic agent corresponding to the same SSA labeled with ^{111}In or ^{68}Ga , which is now preferred for molecular imaging of PPGL. PRRT with ^{177}Lu was pioneered by the Erasmus group who demonstrated highly favorable results in a large cohort of NET patients. Despite the impressive results achieved using these approaches, this therapy was initially performed only in academic centers and used on a compassionate basis. This limitation led the results to be scarce, prohibiting the establishment of an evidence base that typically accompanies registration and approval of cancer therapies. This drawback was recently addressed by studies done on midgut NETs following the recent release of NETTER-1 results. In NETTER-1, ^{177}Lu -DOTATATE (4 administrations of 7.4 GBq every 8 weeks) with an augmented dose of 30 mg octreotide long-acting release (LAR) formulation every 4 weeks was compared to 60 mg octreotide LAR only in patients with

progressive SSTR expressing midgut NETs (ileal in 75% of patients) (Strosberg *et al.* 2017). The interim analysis was encouraging for ^{177}Lu -DOTATATE, with an objective response of 18 vs 3% compared to octreotide alone, with median progression-free survival (PFS) not yet reached in ^{177}Lu -DOTATATE group vs 8.4 months using an augmented-dose of octreotide LAR. There was a reduced mortality in the PRRT arm (14 vs 26 deaths in control arm) which represented a 60% lower estimated risk of death in PRRT arm than in control arm and hazard ratio for death with PRRT vs control arm being 0.4 ($P=0.004$). Importantly, for an essentially palliative therapy, the toxicity profile of PRRT was acceptable and quality of life of patients was increased (Strosberg *et al.* 2018). In a retrospective study, survival and response rates of addition of cold SSA to PRRT as a combination and/or maintenance therapy were evaluated and compared with PRRT alone in 168 patients of advanced gastroenteropancreatic NETs. The patients were divided into two groups: group 1 received PRRT alone (81 patients) and group 2 (87 patients) received PRRT combined with SSA followed by SSA as maintenance therapy or PRRT followed by SSA as maintenance therapy. The median PFS and OS was found to be significantly higher in group 2 (48 and 91 months, respectively) compared with group 1 (27 and 47 months, respectively). This showed the potential role of SSA as a combination and/or maintenance therapy in tumor control of gastroenteropancreatic NETs who underwent PRRT (Yordanova *et al.* 2018). These data have provided a valuable impetus for studying the wider application of the $^{68}\text{Ga}/^{177}\text{Lu}$ -DOTATATE strategy in the management of NETs and various SSTR-expressing tumors.

Prognostic markers for PRRT in NET

The main predictors of poor OS outcome after PRRT are non-specific and include high Ki-67 index (greater than 10%), high uptake on ^{18}F -FDG, involvement of more than two organ systems, local vs distant metastases, low Karnofsky performance score ($\leq 70\%$), high tumor burden, identified progressive disease after first PRRT, and when PRRT is delivered as salvage therapy after chemotherapy (Delpassand *et al.* 2014, Ezziddin *et al.* 2014, Bodei *et al.* 2015b, Kesavan & Turner 2016, Gabriel *et al.* 2019, Wolf *et al.* 2019). In another study, highly elevated maximum standardized uptake values (SUV_{max}) on pre-therapeutic ^{68}Ga -DOTATOC were associated with tumor shrinkage, reduction of tumor markers, and improved overall clinical

condition after PRRT with ^{90}Y -DOTATOC (Oksuz *et al.* 2014). Elevated baseline inflammation-based index (IBI) score (derived from serum C-reactive protein and albumin levels) and persistently elevated IBI between PRRT cycles were also associated with inferior PFS and OS in one small retrospective study in metastatic NETs (Black *et al.* 2019).

Toxicity profiles of PRRT

Toxicity is limited, especially when using ^{177}Lu due to its lower tissue penetration range compared with ^{90}Y (Table 2).

There is an extensive experience on safety of PRRT in NET patients and generally it is found to be well tolerated. Usually nausea and vomiting are the commonly seen acute side effects which could primarily be attributed to amino acid infusions concurrently administered with ^{177}Lu -DOTATATE (Strosberg *et al.* 2017). Fatigue and abdominal pain can also be accompanied; however, they are usually mild and self-limiting (Strosberg *et al.* 2017). Hematotoxicity and nephrotoxicity have been commonly identified adverse events in patients undergoing PRRT. There have been large patient series that reported grade 3/4 nephrotoxicity ranging from 0% (0/343) with ^{177}Lu (Bergsma *et al.* 2016b); 0.3% (20/581) with ^{177}Lu (Brabander *et al.* 2017); 1.3% (1/74) with ^{177}Lu (Sabet *et al.* 2014); and to 1.5% (12/807) with ^{90}Y , ^{177}Lu , or $^{90}\text{Y}+^{177}\text{Lu}$ (Bodei *et al.* 2015a). Further in six patients with a single functional kidney, no acute renal toxicity was reported; however, two patients showed reduction of glomerular filtration rate (5.3 and 13.8%, respectively) with 3–5 cycles of ^{177}Lu demonstrating that it is feasible to treat NET patients having single functioning kidney with ^{177}Lu (Ranade & Basu 2016). Moreover, Bergsma *et al.* also observed that none of the risk factors (hypertension, diabetes, high cumulative injected activity, radiation dose to the kidneys and CTCAE grade) at baseline had a significant effect on renal function over time (Bergsma *et al.* 2016b), whereas another study recommended clinical screening of patients undergoing PRRT in regard to pre-existing risk factors such as hypertension and diabetes and suggested patients

to undergo a thorough dosimetric study and should not receive a biologically effective dose higher than 28 Gy (Bodei *et al.* 2008). The grade 3/4 hematotoxicity reported in large patient series ranged from 9.5% (77/807) with ^{90}Y , ^{177}Lu , or $^{90}\text{Y}+^{177}\text{Lu}$ (Bodei *et al.* 2015a); 10% (61/582) with ^{177}Lu (Brabander *et al.* 2017); 11% (34/320) with ^{177}Lu (Bergsma *et al.* 2016a); and to 11.3% (23/208) with ^{177}Lu (Sabet *et al.* 2013a). In a meta-analysis comprising 16 studies, short-term myelotoxicity was observed in 10% (221/2104) with PRRT monotherapy. At the same time the grade 3/4 hematotoxicity was observed in 10.2% (7/68) of NET patients treated with ^{177}Lu (Sabet *et al.* 2013b) having bone metastases and no hematotoxicity apart from grade 1 anemia in one out of six NET patients treated with ^{177}Lu (Basu *et al.* 2016) having extensive bone marrow involvement shows that PRRT is well tolerated in this group of patients. Furthermore, MDS or AL were reported to range from 1.4% (3/208) with ^{177}Lu (Sabet *et al.* 2013a); 2.0% (22/148) with ^{90}Y or ^{177}Lu (Baum *et al.* 2018); 2.2% (13/582) with ^{177}Lu (Brabander *et al.* 2017); and to 1.4% (32/2225) in the meta-analysis comprising 16 studies (Kesavan & Turner 2016). The identified risk factors for hematotoxicity were impaired renal function, low white blood cell count, extensive tumor mass, high tumor uptake on the scans and/or advanced age, cumulative administered activity (>29.6 GBq) and initial cytopenias, prior number of therapies, prior chemotherapy (alkylating agents), and prior radiotherapy (Sabet *et al.* 2013a, Bergsma *et al.* 2016b, Kesavan & Turner 2016). At the same time, a clear correlation between dose and occurrence of therapy-related myeloid neoplasms could not be established in a cohort of 34 dosimetry assessed patients (Bodei *et al.* 2015a). Neither the administered radioactive dose nor the type of radionuclide was found to have a significant impact on occurrence of marrow neoplasms suggesting that intrinsic, genetically determined factors may potentially play a critical role in the pathobiology of therapy-related myeloid neoplasms (Bodei *et al.* 2015a, 2016). Recently, grade 3/4 hepatotoxicity in NET patients with liver metastases was observed in 3% (20/581) with ^{177}Lu (Brabander *et al.* 2017) and any hepatotoxicity in

Table 2 Beta-emitting radionuclides for targeted radionuclide therapy.

Radionuclide	Half-life (days)	Max energy of emitted particle (MeV)	Path length (mm) Max-Mean	Useful γ for post-therapy imaging
^{177}Lu	6.7	0.5	2.2–0.3	Yes
^{90}Y	2.7	2.3	11.9–2.5	No
^{131}I	8	0.81	2.4–0.3	Yes

d, days; ^{131}I , Iodine-131; ^{177}Lu , Lutetium-177; MeV, mega electron volt; mm, millimeter; ^{90}Y , Yttrium-90.

10.8% (10/93) with either of ^{90}Y or ^{177}Lu or $^{90}\text{Y}+^{177}\text{Lu}$ based PRRT (Riff *et al.* 2015). Also, cardiotoxicity was reported for the first time in a patient with cardiac metastases having normal heart function before therapy; however, he developed new-onset cardiomyopathy following two cycles of ^{177}Lu with persistent cardiac dysfunction for 3 years after PRRT (Hendifar *et al.* 2018). Also, repeated PRRT with eight or more cycles having median administered activity of 63.8 GBq (range 52–96.6) was found to be safe and well tolerated without any life-threatening adverse events (grade 4) (Yordanova *et al.* 2017). It was also observed that the frequency of nephrotoxicity and hematotoxicity was highest with ^{90}Y followed by $^{90}\text{Y}+^{177}\text{Lu}$ and least with ^{177}Lu based PRRT (Bodei *et al.* 2015a). Further, in a prospective trial of 65 gastroenteropancreatic-NET patients treated with four cycles of 7.8 GBq ^{177}Lu -octreotate in combination with 1650 mg/m² capecitabine ($n=28$) and 1500 mg/m² temozolomide ($n=37$), the addition of radiosensitizing chemotherapy did not significantly increase the modest reversible hematotoxicity of PRRT (Kesavan *et al.* 2014).

Several unidentified individual susceptibilities to radiation-associated disease have also been reported (Bodei *et al.* 2015a). PRRT may be associated with renal or hematological (bone marrow) toxicities that can be minimized by adequate precautions and proper and safe dosing (Bodei *et al.* 2014a,b, Brabander *et al.* 2017, Bergsma *et al.* 2018).

Although not randomized, the Erasmus group experience also reported a good tumor response rate in patients with SSTR expressing metastatic bronchial and pancreatic NETs with limited severe long-term toxicities, leukemia or MDS being observed in 2% of patients (Brabander *et al.* 2017).

PRRT in PPGL

The use of PRRT for patients with PPGLs who had high tumor SSTR expression has mainly been reported in retrospective small case series or case reports (only three single-center prospective studies) (Table 2). Overall, after PRRT, 89.8% (95% CI: 84.1–95.0%) of pooled patients had achieved disease stabilization/partial response of inoperable/metastatic PPGL with symptomatic improvement in the vast majority of patients (Figs 4 and 5). No statistically significant heterogeneity among included studies was found ($I^2=37.6\%$, $P=0.099$). Importantly, disease status at the time of therapy is not always well described in the studies (Table 3).

Figure 4

^{177}Lu -DOTATATE in a *SDHB* patient with metastatic jugular paraganglioma (PGL). (A, B) Post-therapy SPECT/CT following the first administration of ^{177}Lu -DOTATATE. (A) SPECT/CT fusion images centered over the jugular PGL (long arrow). (B) Volume rendering (jugular PGL: long arrow, metastases: short arrows). (C) Pre-therapeutic MRI. (D) Post-therapeutic MRI (2 months following the fourth cycle of ^{177}Lu -DOTATATE) showing a tumor shrinkage (asterisk).

Treatment response to PRRT has been evaluated in several ways in the included studies as reported in Table 3 (i.e. by using morphological and/or functional and/or clinical data). Nevertheless, we did not find a significant heterogeneity ($P<50\%$) in the performed meta-analysis about the proportion of response or stable disease after PRRT. Therefore, it is unlikely that the different methods used for evaluating treatment response can influence the pooled results. Even if sometimes combined treatment was performed (as reported in an added column in Table 3), it is unlikely that this has influenced the pooled results on PRRT due to the mild statistical heterogeneity that we have detected among studies.

Van Essen *et al.* treated 12 patients with metastatic PGLs (five with head and neck lesions) with ^{177}Lu -DOTATATE. Six patients showed stable disease, two patients showed response, three patients showed progressive disease and data was unavailable for one patient. However, separate results between tumor locations were not provided (van Essen *et al.* 2006). Forrer *et al.* reported the response rates of PRRT using either ^{90}Y -DOTATOC (25 patients) or

Figure 5

Proportion of PPGL patients with partial response or stable disease after PRRT. Plots of individual studies and pooled proportion (with 95% confidence interval) of inoperable/metastatic PPGL patients with response or stable disease after PRRT (random-effects model). The size of the squares indicates the weight of each study. Mild heterogeneity among studies was evident (I^2 test = 37.6%, $P = 0.099$).

^{177}Lu -DOTATOC (3 patients) in surgically unresectable PPGLs (Forrer *et al.* 2008). The authors reported disease stabilization in approximately 50% of the cohort, a response rate which was considered as inferior compared to their own experience in gastroenteropancreatic NETs.

Treatment response may include locoregional control of the primary tumor and complete disappearance of metastases (Gupta *et al.* 2014). Zovato *et al.* had treated four inoperable hereditary HNPGLs with ^{177}Lu -DOTATATE (three to five courses) and all had stable disease or partial response documented on SSTR imaging (Zovato *et al.* 2012).

Puranik *et al.* in Bad Barka included nine patients with inoperable HNPGLs including two patients previously treated by radiotherapy 13 months earlier (Puranik *et al.* 2015). All tumors had marked avidity for ^{68}Ga -DOTATOC on PET imaging. Eight patients had jugular PGL with tumor multifocality in four patients with coexistence of thoracic PGL in two patients and thoraco-abdominal PGLs in one patient. One patient with a large vagal PGL (and multifocality) had painful bone metastases. The radiopharmaceutical used was either ^{90}Y -DOTATATE (five patients) or combination of ^{90}Y -DOTATATE and ^{177}Lu -DOTATATE (four patients). The number of treatment courses ranged from 2 to 4. Based on ^{68}Ga -DOTATOC PET/CT, four patients showed partial metabolic response (PR, 15–25% decrease in SUV_{max}) and the remaining five patients showed stable disease (SUV_{max} in target lesions – 15–25%). Patients with partial metabolic response had small reductions in tumor size, but insufficient to achieve morphological partial response criteria. No new lesions were found in any patient, but they did not describe the clinical course of the disease, and it is probable that these tumors had slow or minimal progression prior to entering the study. Symptomatic improvement was observed in all six patients and no patients had worsening quality of life. No renal or hematologic toxicity was observed in this series.

Estêvão *et al.* also reported that 90% of patients with jugulotympanic PGLs had symptomatic improvement or stabilization after PRRT (Esteveao *et al.* 2015).

Pinato *et al.* also reported disease stabilization in 3/5, partial response in 1/5, and progressive disease in 1/5 metastatic PGL (five with bone metastases and one with lung metastases), with all being previously documented as progressive disease (Pinato *et al.* 2016).

Kong *et al.* had treated 20 metastatic PPGLs (7 *SDHB*, 1 *SDHD*, 2 without *SDHx*, 10 unknown status) with ^{177}Lu -DOTATATE in two centers (Kong *et al.* 2017). Thirteen patients had sympathetic PPGL, 5 had HNPGL and 2 had both sympathetic PPGL and HNPGL. In 9 patients treated at Peter MacCallum Cancer Centre, the second through fourth cycles were given with radiosensitizing chemotherapy (fluorouracil in three patients, oral capecitabine in one patient, capecitabine/temozolomide in one patient and, temozolomide alone in four patients) unless contraindicated. Response was assessed on ^{68}Ga -DOTATATE PET/CT imaging using a Krenning-like semi-quantitative scale as follows: stable response=unchanged intensity of previous abnormal uptake, partial response=reduction in intensity by 1 Krenning point in at least one tumor site, complete response (total disappearance of abnormal uptake of previously avid lesions), progressive disease (an increase in intensity or extent of previous abnormal uptake or development of new avid lesions). Minor response was also used to describe smaller size changes not meeting partial response criteria on RECIST 1.1 (10% to 30% decrease in maximum diameter of target lesions). Fourteen of 20 patients were treated for uncontrolled secondary hypertension. Among 13/14 with follow-up clinical information, eight required reduced doses of anti-hypertensive medications. Eight of 13 patients had symptomatic improvement and 2/13 had complete resolution of symptoms at 3 months after PRRT. In 7/20 patients with plasma metanephrine/normetanephrine data,

Table 3 Main findings from studies performing peptide receptor radionuclide therapy in patients with inoperable/metastatic pheochromocytoma or paraganglioma (case reports were excluded).

Authors/Year	Country	Type of study	No. of PPGL patients	Progressive disease at baseline	Radiopharmaceutical	No. of cycles	Concomitant treatment	Data used for response assessment	No. of responders (%)	No. of responders or stable disease (%)	Median PFS (months)	Median OS (months)
Kolasinska-Cwikla <i>et al.</i> 2019	Poland	Prospective single center	13	13 (100%)	⁹⁰ Y-DOTATATE	2.5 ^a	–	Morphological	1/12 (8%)	10/12 (83%)	35.0	68.0
Vyakarnanam <i>et al.</i> 2019	Sweden	Retrospective single center	22	9 (41%)	¹⁷⁷ Lu-DOTATATE	3–11	–	Morphological, biochemical, and clinical data	2/22 (9%)	22/22 (100%)	21.6	49.6
Zandee <i>et al.</i> 2019	Netherlands	Retrospective single center	30	20 (67%)	¹⁷⁷ Lu-DOTATATE	4	–	Morphological, and clinical data	7/30 (23%)	27/30 (90%)	30.0	N.A.
Yadav <i>et al.</i> 2019	India	Retrospective single center	25	21 (84%)	¹⁷⁷ Lu-DOTATATE	2–8	Ch (100%)	⁶⁸ Ga-DOTA-SSA PET/CT, morphological, biochemical, and clinical data	7/25 (28%)	21/25 (84%)	32.0	N.A.
Kong <i>et al.</i> 2017	Australia Israel	Retrospective bicentric	20	6 (30%)	¹⁷⁷ Lu-DOTATATE	1–4	Ch (45%)	⁶⁸ Ga-DOTA-SSA PET/CT, morphological, biochemical, and clinical data	8/17 (47%)	15/17 (88%)	39.0	N.A.
Nastos <i>et al.</i> 2017	UK	Retrospective single center	13	13 (100%)	¹⁷⁷ Lu- ⁹⁰ Y-DOTATATE	1–4	Ch, RT or SSA in some cases	Morphological, biochemical, and clinical data	N.A.	13/13 (100%)	38.5	60.8
Pinato <i>et al.</i> 2016	UK	Case series	5	5 (100%)	¹⁷⁷ Lu-DOTATATE	1–4	–	⁶⁸ Ga-DOTA-SSA PET/CT, and morphological data	1/5 (20%)	4/5 (80%)	17.0	N.A.
Estevao <i>et al.</i> 2015	Portugal	Retrospective single center	14	4 (29%)	¹⁷⁷ Lu-DOTATATE	3	–	⁶⁸ Ga-DOTA-SSA PET/CT, and clinical data	10/14 (71%)	10/14 (71%)	N.A.	N.A.
Puranik <i>et al.</i> 2015	Germany	Prospective single center	9	N.A.	¹⁷⁷ Lu- ⁹⁰ Y-DOTATATE/ DOTATOC	2–4	–	⁶⁸ Ga-DOTA-SSA PET/CT, morphological, and clinical data	4/9 (44%)	9/9 (100%)	N.A.	N.A.
Zovato <i>et al.</i> 2012	Italy	Case series	4	4 (100%)	¹⁷⁷ Lu-DOTATATE	3–5	–	SSA scintigraphy, morphological, and clinical data	2/4 (50%)	4/4 (100%)	N.A.	N.A.

(Continued)

Table 3 Continued.

Authors/Year	Country	Type of study	No. of PPGL patients	Progressive disease at baseline	Radiopharmaceutical	No. of cycles	Concomitant treatment	Data used for response assessment	No. of responders (%)	No. of responders or stable disease (%)	Median PFS (months)	Median OS (months)
Imhof <i>et al.</i> 2011 ^b	Switzerland	Prospective single center	39	39 (100%)	⁹⁰ Y-DOTATOC	1–10	-	SSA, scintigraphy, morphological, biochemical, and clinical data	7/39 (18%)	N.A.	N.A.	N.A.
Forrer <i>et al.</i> 2008	Switzerland	Retrospective single center	28	28 (100%)	¹⁷⁷ Lu- ⁹⁰ Y-DOTATOC	1–4	-	Morphological, biochemical, and clinical data	7/28 (25%)	20/28 (71%)	N.A.	N.A.
van Essen <i>et al.</i> 2006 ^c	Netherlands	Retrospective single center	12	4 (33%)	¹⁷⁷ Lu-DOTATATE	4	-	Morphological, biochemical, and clinical data	2/11 (18%)	8/11 (73%)	N.A.	N.A.

^aThe study reports mean number of ⁹⁰Y-DOTATATE PRRT cycles per patient and does not provide the range of cycles; ^bStudy not included in the meta-analysis for possible patient overlap with the study of Forrer *et al.*; ^cstudy not included in the meta-analysis for possible patient overlap with the study of Zandee *et al.*

Note: response assessment criteria usually included various combinations of imaging (morphological and/or ⁶⁸Ga-DOTA-SSA PET/CT), biochemical, and clinical data as mentioned in the table.

plasma metanephrine and/or normetanephrine decreased in 6/7 patients, whereas plasma chromogranin A (CgA) decreased in 12/14 patients with available plasma CgA data. Among the 17/20 patients evaluable for SSTR response, 8 (47%) had a partial response, 7 (41%) had stable disease, and 2 (12%) had disease progression. Of the 14/20 patients with available and evaluable disease by RECIST 1.1, 4 (29%) had partial RECIST response, 1 (7%) had minor morphologic regression, 7 (50%) had stable disease, and 2 (14%) had progression. Median PFS was 39 months; median OS was not reached (five deaths; median follow-up, 28 months). Four and two patients had grade 3 lymphopenia and thrombocytopenia, respectively. Renal impairment in two patients were attributed to underlying amyloidosis, one not described). Hypertension flare was observed in one patient, 3 h after PRRT administration. No additional toxicity was apparent with its concomitant use of radiosensitizing chemotherapy. Further, four patients who progressed or deteriorated with tumor progression or had recurrence of hypertension following first cycle of PRRT were re-treated with additional cycles of PRRT ranging from 1 to 8 cycles. Two patients were provided additional maintenance therapies for persisting disease with further favorable response.

Nastos *et al.* had described the outcomes of 22 patients with progressive/metastatic PPGLs treated with either ¹³¹I-MIBG (11 patients), ⁹⁰Y-DOTATATE (8 patients), ¹⁷⁷Lu-DOTATATE (1 patient) or combination of ¹³¹I-MIBG with ⁹⁰Y/¹⁷⁷Lu-DOTATATE (2 patients) (Nastos *et al.* 2017). They have shown a response in 11 of 11 (100%) treatments with ⁹⁰Y-DOTATATE alone or in combination and a mean PFS of 43 months. In the subgroup of 15 patients with extrarenal PGLs (21 treatments, from which 13 were with PRRT and 8 with ¹³¹I-MIBG), PRRT performed significantly better than ¹³¹I-MIBG in terms of OS, PFS, and response to treatment. Four patients (18.1%) developed renal toxicity related to radionuclide treatment, with grade 3 renal toxicity in a patient treated with ⁹⁰Y-DOTATATE and ¹³¹I-MIBG. Although this study mainly relies on the use of ⁹⁰Y-DOTATATE for PRRT, it illustrates that SSTR-directed targeted radionuclide therapy should therefore be favored over ¹³¹I-MIBG in this subgroup of patients.

In a retrospective study by Zandee *et al.*, 30 inoperable or metastatic PPGL patients underwent PRRT with upto four cycles of ¹⁷⁷Lu-DOTATATE (7.4 GBq/cycle) (Zandee *et al.* 2019). Twenty of 30 patients treated were progressive at start. According to RECIST 1.1, 7 (23.3%) patients had partial response and 20 (66.7%) patients had stable disease, whereas 3 (10%) patients had progressive disease.

In 20 patients with baseline disease progression, tumor control was observed in 17 (85%). Median PFS was 30 months and median OS was not reached (nine deaths; median follow-up, 52.5 months). Grade 3/4 subacute hematotoxicity occurred in 6 (20%) patients. One patient developed MDS after 45 months following six cycles of ^{177}Lu -DOTATATE (including retreatment, cumulative dose 44.4 GBq) and died after 4.5 years of first cycle of PRRT due to complications. This patient was not treated with any prior chemotherapy or ^{131}I -MIBG therapy and lacked bone marrow metastases. A reversible subacute adverse event due to cardiac failure following possible catecholamine release/crisis occurred in two patients (6.7%).

In a recently published retrospective study by Vyakaranam *et al.*, 22 patients received ^{177}Lu -DOTATATE ($n=3$ with four cycles of 7.4GBq and $n=19$ with dosimetry-guided PRRT where as many cycles (3–11) were administered until 23Gy to the kidneys or 2Gy to bone marrow was reached) achieving a median OS of 49.6 (range 8.2–139) months and a median PFS of 21.6 (range 6.7–138) months (Vyakaranam *et al.* 2019). Nine of 22 patients treated were progressive at start. According to RECIST 1.1, two (9.1%) patients had partial response, 20 (90.9%) patients had stable disease. Among the nine progressive patients at the start of PRRT, one achieved partial response and eight stable diseases with a median decrease of 14% (range 0–56%) in tumor size. The biochemical response was evaluated with a reduction in catecholamines in 11 of 12 evaluable patients (91.6%) with >50% reduction in 3/12 (25%) of patients, whereas increase in catecholamines was observed in 1/12 (8.3%) patients. Further, a reduction in CgA was observed in 13 of 15 evaluable patients (86.7%) with >50% reduction in 6/15 (40%) of patients, whereas increase in CgA was observed in 2 (13%) patients. Thus, biochemistry indicated progressive disease in two patients with stable disease on CT/MRI but, in the remaining patients, the biochemical and morphological responses were in agreement. Ten of 22 patients had catecholamine-related symptoms, which in two were aggravated during PRRT, including the development of hypertensive crisis. No renal toxicity and only grade 1 ($n=10$) or grade 2 ($n=6$) hematological toxicity was reported in 16/22 (73%) patients. High Ki-67 (>15%) and prior PRRT therapy because of progression constituted negative predictive factors for OS, whereas only high Ki-67 (>15%) constituted negative predictive factor for PFS.

In a recently published prospective study by Kolasinska-Cwikla *et al.*, 13 inoperable or metastatic SDHx-related PPGL patients (SDHB, $n=5$; SDHD, $n=8$) underwent a 2.5 mean cycles of ^{90}Y -DOTATATE (mean 3.4 GBq/cycle)

(Kolasinska-Cwikla *et al.* 2019). All 13 patients treated were progressive at start. According to RECIST 1.0, after 1 year of PRRT therapy, nine (82%) of 11 patients had stable disease, whereas 2/11 (18%) patients had progressive disease and none of the patients demonstrated partial response. Grade 3 renal toxicity occurred in two patients who also demonstrated grade 3 anemia. Median PFS and OS were 35 and 68 months, respectively; however, they were 12 and 25 months, respectively for SDHB patients and did not reach for SDHD patients. The OS was 25 months and PFS was 10 and 12 months for patients with liver and bone metastases, respectively. In long-term follow up (duration unspecified), all SDHB patients and 3 SDHD patients progressed with 4 (80%) deaths in SDHB and 2 (25%) deaths in SDHD patients.

In a retrospective study by Yadav *et al.*, 25 patients received a median of 3 (range: 2–8) cycles of PRRT with ^{177}Lu -DOTATATE and concomitant capecitabine (1250mg/m² for 15 consecutive days commencing on the morning of ^{177}Lu -DOTATATE therapy) (Yadav *et al.* 2019). According to RECIST 1.1, 7 (28%) patients had partial response, 14 (56%) patients had stable disease, and the remaining 4 (16%) patients had progressive disease. The biochemical response was evaluated with a reduction in CgA observed in 23 (92%) of patients with >50% reduction in 7 (28%) of patients, whereas increase in CgA was seen in 2 (8%) patients. The symptomatic response was evaluated by change in anti-hypertensive drugs. Fourteen of 25 patients were on anti-hypertensive drugs and its reduction was observed in 6 (43%) patients, whereas no change occurred in 8 (58%) patients. The median PFS was 32 months and the median OS was not reached (seven deaths); however, the median OS in progressive group was 16 months (95% CI, 14–24 months). All the patients reported improved general well-being without any severe hematotoxicity or nephrotoxicity. They concluded that concomitant therapy did not demonstrate superiority in comparison to reported outcomes of published PRRT monotherapy. Furthermore, a case report describing metastatic mediastinal PGL improved by combination of ^{177}Lu -DOTATATE and capecitabine has also been reported (Ashwathanarayana *et al.* 2017).

In conclusion, overall results suggest favorable objective disease control, reflected mainly by partial response or stable disease (Fig. 5). The rate of objective response on conventional imaging seems to be lower than that for gastroenteropancreatic NETs. One could speculate about possible lower radiosensitivity of PPGL, but this question cannot be answered currently and would require specific prospective evaluation. Patients should

undergo both ^{123}I -MIBG and ^{68}Ga -DOTA-SSA imaging, and based on the results, the first-line therapy should be chosen (Vyakaranam *et al.* 2019). In case of mosaic expression of the two tracers, treatment with both can be considered, and if any lesion/s lack uptake of both the tracers, then it can be targeted by additional beam radiation (Vyakaranam *et al.* 2019). Furthermore, PRRT with combined and/or maintenance cold SSA therapy should be considered as it demonstrated superior results compared to PRRT monotherapy in NETs (Yordanova *et al.* 2018). However, currently there are no data supporting this in the setting of PPGL. These data have provided a valuable impetus for studying the wider application of the $^{68}\text{Ga}/^{177}\text{Lu}$ -DOTATATE strategy in the management of NETs and various SSTR-expressing tumors.

Given the favorable efficacy, further prospective PRRT trials, including use of radiosensitizing chemotherapy, are warranted. There is currently an ongoing phase II study at the NIH (NCT03206060) that evaluates ^{177}Lu -DOTATATE for metastatic/inoperable *SDHx* and apparently sporadic PPGLs. Interestingly, inclusion requires progressive disease by RECIST 1.1 with or without symptoms within the last 12 months. The primary objective relies on 6-month PFS. Further, future prospective trials comparing PRRT and HSA ^{131}I -MIBG therapy determining their efficacy and radiation safety profile should be studied.

Potential indications of radiotherapeutic in the management of PPGL

Head and neck PGL

Most HNPGLs exhibit an indolent behavior and almost always do not secrete catecholamines and hence need not always show symptoms of catecholamines excess. The application of targeted internal radiotherapy should therefore be discussed in limited situations in non-metastatic patients. In a large HNPGL, surgical management is often challenging due to complex anatomy and proximity to critical structures. This is particularly true for jugular PGLs arising from the adventitia of the dome of the jugular bulb (glomus jugulare PGLs) that may extend into the pars nervosa of the jugular foramen, jugular vein, sigmoid sinus, carotid artery, middle ear, mastoid space, and posterior cerebellar fossa. In few patients, subtotal surgical resection can be considered for limiting cranial nerve morbidity. Surgery of vagal nerve PGL is also questionable since it always requires the sacrifice of the vagus nerve. In recent years, various forms

of radiotherapy have been reported in these tumors, with favorable outcomes. Vagal nerve PGL is usually related to *SDHx* mutation (mainly *SDHD*) in approximately 40% of patients. The impact of detecting multiple HNPGLs, even millimetric in size, is of a major clinical importance. It is important to recall that bilateral neurologic injuries affect respiration, deglutition and phonation and are associated with chronic complications and vital risks (Suarez *et al.* 2013). In these patients with tumor multifocality, any post-operative complications may compromise subsequent interventions. The initial staging of an HNPGL is currently based on the use of anatomical and functional imaging approaches to determine the tumor extension into the bone and surrounding soft tissue, to determine tumor multiplicity not only in the head and neck area but also elsewhere in the body, and finally, to exclude any metastases. Although the locoregional extension of HNPGLs is well determined and delineated by anatomic imaging (temporal bone CT, MR angiography), PET imaging using specific tracers performs better for detecting multiple lesions and can increase diagnosis confidence for tumor extensions classified as doubtful on anatomic imaging. Furthermore, previous treatments can lead to artifacts that can seriously degrade the quality of anatomic imaging.

An individual management approach is absolutely necessary in HNPGL patients, especially those with multifocality with vagus nerve involvement. In all patients, a wait-and-scan policy could be the primary option for defining the growth pattern. Patients undergoing such an approach should be informed that many tumors continue to grow, and may eventually require treatment. In head and neck due to the presence of important structures and nerves, at times even a minor growth may lead to symptoms and complications. External beam radiotherapy (EBRT) should be considered as an option in patients with inoperable HNPGL (i.e. unresectability of the primary tumor or tumor relapse due to invasion into surrounding tissue) having progressive and/or symptomatic disease. It has been reported that higher doses are associated with improved local control (Vogel *et al.* 2014, Breen *et al.* 2018). The advantage of PRRT over radiotherapy is potentially to treat multiple tumors during the same session without any risk of nerve palsy. In patient with a single inoperable HNPGL, the indication of systemic PRRT vs locoregional treatment with EBRT needs to be discussed on an individual basis, depending on potential benefits and estimated risks of both strategies. EBRT can be provided first and PRRT could be given in cases who progress on EBRT. PRRT possibly could act synergistically

after debulking surgery of large PGL since it may have more limited effect on very large tumors. In cases of large PGL, PRRT with ^{90}Y only or alternating it with ^{177}Lu to prevent higher renal toxicity can be considered.

Retroperitoneal PPGL

The majority of these patients are clinically symptomatic due to catecholamines excess which may get controlled by surgery, regardless of the surgical approach (open or endoscopic). Although minimally invasive surgery can also be performed in most retroperitoneal PGLs, surgery can be more challenging due to possible adhesions to major retroperitoneal vessels leading to surgical conversions. Therefore, surgical strategy should be tailored to each situation with the knowledge of the genetic status since upto 70% of patients with extra-adrenal retroperitoneal PGL may carry germline mutations in *SDHx* or *VHL* genes (Gimenez-Roqueplo *et al.* 2003, Neumann *et al.* 2004, Amar *et al.* 2005, 2007, Brouwers *et al.* 2006). Large PPGLs and those associated to *SDHB* mutation are associated with a higher risk for metastatic spread and imaging is required to fully localize the extent of disease at whole-body scale. Surgery should always be considered as first-line therapy. In patients with non- or incompletely resectable large PGL, a radiotherapeutic management could be considered (also as complementary therapy after debulking surgery), especially for patients with *SDHB* mutation which are prone to develop metastases and symptomatic patients (e.g. pain, uncontrolled hypertension). The choice of the therapeutic radiopharmaceutical can be tailored to diagnostic scans using their uptake pattern on companion diagnostics. The use of PRRT using ^{177}Lu -DOTA-SSA will be better suited to *SDHx*-related PPGL than ^{131}I -MIBG.

Metastatic PPGL

The management of patients with metastatic PPGL can be challenging and may rely on surgery, interventional radiology, chemotherapy, external beam radiation, or other therapeutic options (Nolting *et al.* 2019). Primary tumor resection can be recommended based on careful evaluation of tumor burden as well as the extent of metastatic disease. Exercising this option helps to reduce cardiovascular and other such risks from high catecholamine levels and alleviate/prevent symptoms from the tumor's invasion of surrounding structures. Treatment of metastases with a curative intent to treat may also be considered in individual patients with oligometastatic disease which remains a rare situation.

In rapidly progressive metastatic PPGL, patients can be treated with various chemotherapeutic agents. Although there exist various options as well as biases in the literature, currently CVD is still considered as the first-line therapeutic modality, especially for rapidly progressive disease (Niemeijer *et al.* 2014). In *SDHB* patients, temozolomide may be considered for tumor stabilization as a maintenance regime subsequent to CVD chemotherapy (Hadoux *et al.* 2014). Sunitinib is currently under evaluation (NCT01371201). Palliative surgery followed by external radiotherapy can be indicated in metastatic PPGL with a high risk for neurologic compression (e.g. spinal cord compression). In metastatic PPGL with slow pace of growth and limited tumor volume, ^{131}I -MIBG or PRRT using ^{177}Lu -DOTA-SSA can be indicated in patients with positive scans for the respective radiopharmaceuticals. Additionally, combined ^{177}Lu -DOTA-SSA and cold SSA can be considered in SSTR positive patients and its efficacy can be determined in future trials. However, currently there are no data supporting this in the setting of PPGL. Moreover, patients with tumor phenotype showing both or discordant molecular targets on various lesions may theoretically benefit from a combined or sequential radionuclide therapeutic approach using PRRT and ^{131}I -MIBG, but further trials are required to assess efficacy and potential toxicity of this regimen.

Healthcare environment

Management of PPGL is complex and it is therefore strongly encouraged to refer these patients to experienced centers with high-volume surgical procedures. Core members of the team should include various specialities (oncologists, radiation oncologists, endocrinologists, otorhinolaryngologist/endocrine surgeons, radiologists/nuclear physicians, pediatricians, clinical geneticists, and pathologists) who work in the same center and have meetings on the regular basis. Imaging scans can be performed elsewhere if available and then can be interpreted by this core team.

Research avenues

Dosimetry-based regimens

Dosing of targeted radionuclides is often based on empirical observations and is not subject to the precise, patient-specific treatment planning that is standard for external beam radiotherapy. Based on published studies,

it is possible that better outcomes could be achieved with increased cumulative dose delivery to tumors. The main challenge for systemic radiation therapy remains to optimize the dose delivery to a tumor, while minimizing normal tissue irradiation. In therapeutic nuclear medicine, the term 'dose' is a misnomer that is often used for describing the administered activity (expressed in units of Becquerel (Bq)) of a radiopharmaceutical. The 'absorbed dose' (expressed in units of gray (Gy)) is dependent on many factors including the administered activity but most importantly on tumor characteristics (target expression, metabolic activity, volume, and perfusion). Calculation of the absorbed dose is more complex than for external radiotherapy since the cells and organs are irradiated not only for seconds or minutes, but continuously, over a long period of time with everchanging dose rate. Therefore, it relies on repeated blood/urinary collections and imaging procedures following therapy. Several modern dosimetry models have been developed in order to optimize PRRT for individual patients (Taïeb *et al.* 2015, Del Prete *et al.* 2018, Huizing *et al.* 2018). In order to circumvent some difficulties for estimating the absorbed dose by the tumor, two main options have been proposed for achieving radiation dose intensification (Cremonesi *et al.* 2018). One is the standard 7.4 GBq per cycle with variation in number of cycles until the individual limit of kidney/bone marrow biologic effective dose is reached (Sandstrom *et al.* 2013, Sundlov *et al.* 2017) or the other is a four fixed cycles with variable activity per cycle to reach the dose limits (Del Prete *et al.* 2017). The time interval between therapeutic cycles could also be tailored to individual situations.

Preliminary results of a trial in NETs (P-PRRT, NCT02754297) have shown that the use of patient-specific PRRT dosimetry might increase absorbed dose delivered to a tumor (median 1.26-fold; range: 0.47–2.7-fold) compared to fixed-dose regimen, without increased toxicity (oral communication OP-181, Del Prete *et al.* 2018). A prospective evaluation of PRRT in PPGL patients with integration of a dosimetry-based approach (at voxel level analysis) would be an important step toward treating PPGL patients. Roadmaps to improvements not only include the use of synergistic effects of radiosensitizers but also knowledge regarding the relationships between tumor genotype and cellular sensitivity to ionizing radiations.

Biomarkers of response to PRRT

Therapeutic response to PRRT is often delayed and post-therapy scans or regular ^{68}Ga -DOTA-SSA PET/CT scans

often show disease stabilization with some clinical and biological improvement. Furthermore, bone metastases are often detectable only on molecular imaging and not measurable according to CT criteria and therefore not evaluable on RECIST. Assessment of response to PRRT would probably require a specific composite scoring with the integration of tumor uptake as a continuous variable. Beyond classical uptake parameters, it is of prime importance to find new biomarkers of response. One of the great advantages of PET relative to other imaging modalities is its inherent quantitative nature. Traditionally, PET image analysis in the field of oncologic applications has been restricted to the use of semi-quantitative indices, such as SUV or SUV-derived indices. Currently, nuclear imaging is ideally placed via radiomics approaches (Kumar *et al.* 2012, Lambin *et al.* 2012, Garcia-Carbonero *et al.* 2015, O'Connor *et al.* 2015). Over the last few years, a lot of interest has been concentrated on the development of PET image segmentation algorithms allowing the robust and reproducible determination of 3D tumor volumes from PET reconstructed images. As such, the use of PET image-derived 3D tumor volumes has in turn increased the potential of further exploring the information available in PET tumor images. Further analysis consists of assessing the PET tumor shape and/or heterogeneity in intratumoral activity. Intratumoral heterogeneity has been found to demonstrate superior prognostic performance in predicting both PFS and OS in 141 patients of NETs (Werner *et al.* 2017) and OS in 31 patients of pancreatic NETs (Werner *et al.* 2019). These new parameters that may reflect, depending upon the radiotracer used, various biological processes that could be used for assessment of response to PRRT (Werner *et al.* 2017, 2019). We can anticipate that combination of radiomics, tumor grade, and molecular biomarkers (e.g. transcriptomics, miRNA, DNA, metabolomics) will offer an optimal multiparametric approach for more individualized management to patients (Bodei *et al.* 2018). It is expected that machine learning technology will help to improve parameter selection and combination compared to more traditional statistical analysis, albeit the need for extensive validation and evaluation across centers and patient populations. Together with dosimetry, these biomarkers of treatment response will enable more individualized treatment plans.

Alpha emitters

Until now, experience with therapeutic applications of nuclear medicine was based on beta-emitting

radionuclides. Beta emitters are characterized by a path length in the range of millimeters and a low linear energy transfer (LET) (Navalkisoor *et al.* 2019). The biological effectiveness of the deposited radiation is inversely correlated with the LET. From a radiobiological standpoint, there are significant advantages of using alpha emitters due to their shorter path length of 40–100 microns and much higher LET (Navalkisoor *et al.* 2019). As a result, alpha emitters deposit much more energy along their path, resulting in greater cytotoxicity than seen with beta radiation, which manifests itself through mechanisms such as apoptosis, autophagy, necrosis, and mitotic catastrophe (Baidoo *et al.* 2013, Wadas *et al.* 2014). Until recently, alpha-emitters were only used in experimental settings. PPGL as many NETs present or develop bone metastases, which may lead to adverse skeletal-related events (SRE) including pain and neurological compression (Ayala-Ramirez *et al.* 2013). SREs can lead to significant morbidity, impact functional status, and alter patient's quality of life. The high incidence of osteoblastic metastatic bone disease should allow for the use of bone-seeking radiopharmaceuticals in carefully selected patients who have bone scan-positive lesions. Radium-223 dichloride (^{223}Ra) is a bone-seeking calcium mimetic alpha emitter that accumulates in areas of increased bone turnover and has been approved for the treatment of metastatic prostate cancer to the bone. Following the results of the ALSYMPCA (ALpharadin in SYMptomatic Prostate CANcer) Phase III ^{223}Ra multinational trial (Parker *et al.* 2013), the FDA granted full approval in May 2013 with subsequent approval by the European Union. In contrast to other bone-seeking radiopharmaceuticals, ^{223}Ra therapy demonstrates significant survival improvements compared to the placebo. New clinical trials are underway to examine ^{223}Ra efficacy in breast cancer, lung cancer and osteosarcoma. Further studies are necessary to specifically assess the role of ^{223}Ra in palliation of extensive metastatic bone disease in endocrine malignancies such as PPGL, which present with bone lesions in more than 50% of metastatic patients (Zelinka *et al.* 2008). A case report has shown an improvement in pain control, mobility, and overall quality of life in a 26-year-old woman with extensive bone disease in a *SDHB*-related metastatic PGL treated with ^{223}Ra (Makis *et al.* 2016).

Alpha-particle emitting radiopharmaceuticals have also been evaluated in small series for intra-arterial (IA) PRRT in patients with liver metastases. IA PRRT resulted in a four-fold higher intrahepatic tumor accumulation compared to intravenous infusion due to high first-pass extraction, decreasing to 1.3 times greater at 72h

(Kratochwil *et al.* 2011). In a pilot study of patients (in 6 patients) who previously failed treatment with a beta emitter PRRT, IA therapy with ^{213}Bi -DOTATOC for liver metastases produced durable responses with acceptable toxicity in NETs (Kratochwil *et al.* 2014). By contrast, systemic administration of alpha-particle emitting SSA would possibly be an interesting approach in PPGL but this would require to perform phase I studies in experienced medical centers.

Recently, strong anti-tumor effects of α -emitting meta-211At-astato-benzylguanidine have been reported in a PC12-cell line mouse xenograft PHEO-bearing mouse model (Ohshima *et al.* 2018).

Combined strategy

In the recent years, immunotherapy has gradually gained an important role in oncology. Checkpoint inhibitors (PD-1/PD-L1) have opened up exciting new treatment pathways in metastatic cancers (Galluzzi *et al.* 2018). Predictors of response are multiple (e.g. high mutation burden/neoantigen burden, high PD-L1 expression, and presence of pro-immunogenic driver mutations). A recent study has shown that the expression of PD-L1 and extent of immune infiltration of small bowel NETs is heterogeneous (Cives *et al.* 2019). The effect of PPGL driver mutations on these parameters and response to immunotherapy would be of particular interest. Immunity can be dissected with large-scale technologies (e.g. mutational landscape, transcriptome, major histocompatibility complex-associated peptidome of tumor cells, T-cell receptor repertoire, presence of tumor-infiltrating lymphocytes and its detailed characteristics, evaluation of cytokines, and microenvironment assessment). For tumors with low tumor mutation burden such as NETs, one approach for increasing treatment efficacy would be to increase mutational/neoantigen load (Lawrence *et al.* 2013, Chauhan *et al.* 2018). A preclinical study has shown that PRRT leads to increased infiltration of antigen-presenting cells and natural killer cells into tumors, suggesting a mechanistic role for the inflammatory response followed by increased innate immunity in the action of PRRT (Wu *et al.* 2013). The immunotherapy with external beam radiation, including targeted internal therapy could synergistically play a significant role, which needs to be further evaluated. An emerging challenge is how to combine radiation therapy with immunotherapy effectively (Serre *et al.* 2016, Citrin 2017). In metastatic PPGL, this approach would have to be powered by various studies showing that indeed PPGL have specific

immune targets since they are generally considered as immunogenically cold.

New ligands or targets for PRRT

More recently, there has been an evidence that radiolabeled SSTR2 antagonists generate higher tumor doses and more DNA double-strand breaks than agonists, resulting in better treatment efficacy despite poor internalization. An open-label study to evaluate safety, tolerability, biodistribution, dosimetry and preliminary efficacy of ^{177}Lu -OPS201 for the therapy of somatostatin receptor-positive NETs is currently recruiting patients (NCT02592707). In this clinical trial, malignant unresectable PHEO or PGL are also eligible.

An Evans blue (EB) modification of DOTA-octreotate, resulted in a radionuclide ^{177}Lu -DOTA-EB-TATE which markedly increased binding to circulating serum albumin, a slower clearance through the urinary tract and thus, an increased half-life in blood was observed thereby increasing tumor retention. In a pilot study by Zhang *et al.* in advanced NET patients, ^{177}Lu -DOTA-EB-TATE demonstrated a 7.9-fold increase in delivered tumor doses when comparable total body effective doses of ^{177}Lu -DOTATATE (0.174 mSv/MBq, three patients) and ^{177}Lu -DOTA-EB-TATE (0.205 mSv/MBq, five patients) (Zhang *et al.* 2018). However, significant increase in dose delivery to the kidneys (3.2-fold) and bone marrow (18.2-fold) were noted in patients receiving ^{177}Lu -DOTA-EB-TATE than those receiving ^{177}Lu -DOTATATE (Zhang *et al.* 2018). Subsequently, four NET patients were treated with single low-dose of ^{177}Lu -DOTA-EB-TATE (0.66 gigabecquerel (GBq)) and were compared to a control group undergoing ^{177}Lu -DOTATATE (3.98 GBq, three patients) (Wang *et al.* 2018). The response was evaluated by assessing difference in SUV_{max} of ^{68}Ga -DOTATATE before and 3-month after therapy and no difference was found between ^{177}Lu -DOTA-EB-TATE and ^{177}Lu -DOTATATE groups. Further, the ^{177}Lu -DOTA-EB-TATE group approximately received 1/6 of the total radiation exposure compared to ^{177}Lu -DOTATATE group. Also, single low-dose ^{177}Lu -DOTA-EB-TATE was found to be safe and effective in treatment of NETs. These encouraging results merit further studies with increasing dose and frequency of ^{177}Lu -DOTA-EB-TATE in NETs, including PPGL.

With the expanding use of prostate-specific membrane antigen (PSMA)-based PET imaging, several reports have shown uptake in non-prostatic benign and malignant entities including PGL of urinary bladder in a patient

with metastatic prostate cancer (Parihar *et al.* 2018). Since PSMA targeting represents a theranostic approach, it could be interesting to evaluate PSMA expression in a series of PPGLs with various genotypes.

In conclusion, nuclear medicine has gained an increasing role in the personalized approach to PPGL patients. This has been recently augmented by a number of excellent PET radiopharmaceuticals, which target different functional and molecular pathways that often reflect the diverse genetic landscape of PPGL. The visualization and quantification of tumor targets by imaging at the whole-body level (e.g. somatostatin receptors, norepinephrine transporter, and bone turnover), mirroring 'in vivo immunohistochemistry', enabling selection of candidates for potential targeted radionuclide therapy (Lutathera®, Azedra®, and Xofigo®). The very recently obtained FDA approvals in this area have generated interest by various interest groups from researchers to industries and will give a new impetus to the development of therapeutic radiopharmaceuticals. Despite increased availability of diagnostic and therapeutic radiopharmaceuticals, it is important to remember that management of PPGL is complex and the patients should be referred to experienced centers for their management. The future of therapeutic nuclear medicine will also depend upon the identification of new targets, new schedules, and potential synergistic combinations.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This research 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.

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Received in final form 9 September 2019

Accepted 12 September 2019

Accepted Preprint published online 12 September 2019