15 YEARS OF PARAGANGLIOMA

Imaging and imaging-based treatment of pheochromocytoma and paraganglioma

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Abstract

Although anatomic imaging to assess the precise localization of pheochromocytomas/paragangliomas (PHEOs/PGLs) is unavoidable before any surgical intervention on these tumors, functional imaging is becoming an inseparable portion of the imaging algorithm for these tumors. This review article presents applications of the most up-to-date functional imaging modalities and image-based treatment to PHEOs/PGLs patients. Functional imaging techniques provide whole-body localization (number of tumors present along with metastatic deposits) together with genetic-specific imaging approaches to PHEOs/PGLs, thus enabling highly specific and sensitive PHEO/PGL detection and delineation that now greatly impact the management of patients. Radionuclide imaging techniques also play a crucial role in the prediction of possible radioactive treatment options for PHEO/PGL. In contrast to previous imaging algorithms used for either assessment of these patients or their follow-up, endocrinologists, surgeons, oncologists, pediatricians, and other specialists require functional imaging before any therapeutic plan is outlined to the patient, and follow-up, especially in patients with metastatic disease, is based on the periodic use of functional imaging, often reducing or substituting for anatomic imaging. In similar specific indications, this will be further powered by using PET/MR in the assessment of these tumors. In the near future, it is expected that PHEO/PGL patients will benefit even more from an assessment of the functional characteristics of these tumors and new imaging-based treatment options. Finally, due to the use of new targeting moieties, gene-targeted radiotherapeutics and nanobodies-based theranostic approaches are expected to become a reality in the near future.

Key Words
- positron-emission tomography
- gallium radioisotopes
- somatostatin
- ¹⁸F-DOPA
- ¹⁸F-FDG
Current approaches for localization of pheochromocytomas/paragangliomas

Paragangliomas associated with the parasympathetic nervous system

Glomus tumors and other paragangliomas (PGLs) of parasympathetic origin develop from non-chromaffin organs that act as chemoreceptors and are mainly located in glomus bodies (carotid body, aortic bodies) or embedded in several sensory parasympathetic ganglia. Those located in the head and neck region are referred to as head and neck PGLs (HNPGGLs). Carotid body PGL (CBP) is the most common location among all parasympathetic PGLs, followed by glomus jugulare (the jugular bulb in the jugular foramen, JP), glomus tympanicum or hypotympanicum (middle ear or hypotympanum, TP), and then glomus vagale (VP). The carotid body is a prime example of a chemoreceptor organ that mediates reflex hyperventilation during hypoxemia via activation of the respiratory center in the brain.

Approximately two-thirds of HNPGLs do not usually produce catecholamines but some may produce catecholamines and, if so, almost always produce dopamine, which is converted inside a tumor to 3-methoxytyramine – currently the best specific biomarker in the detection of these tumors (van Duinen et al. 2010, 2013, Eisenhofer et al. 2012). 3-Methoxytyramine, which is elevated in 33% of patients with HNPGLs, supports this conclusion (van Duinen et al. 2010, 2013).

The role of current imaging techniques is mainly to diagnose HNPGL, determine tumor extension into the bone and/or surrounding soft tissue, and rule out the presence of multiple tumors or local metastases, especially in lymph nodes. Evaluation of parapharyngeal space tumors involves careful consideration of clinical and imaging information to distinguish vagal PGLs from peripheral nerve sheath tumors (schwannoma, neurofibroma), nodal metastases (nasopharynx/oropharynx, thyroid cancer), other rare primary tumors, and a variety of uncommon miscellaneous lesions (Taieb et al. 2013).

Anatomic imaging

Anatomic imaging serves as the first-line modality in the locoregional staging of these tumors. HNPGLs usually demonstrate marked enhancement of intra-tumoral vessels following contrast administration on CT, low signal on T1-weighted images, and an intermediate to high signal on T2-weighted MRI images; they also often enhance intensely after gadolinium injection on MRI. Flow signal voids in the tumor are typical of PGL, with a ‘salt-and-pepper’ appearance on spin-echo sequences. Magnetic resonance (MR) angiography also demonstrates intra-tumoral arterial vessels (Johnson 1998, Arnold et al. 2003, van den Berg et al. 2004, van den Berg 2005, Neves et al. 2008). 3D time-of-flight (a non-contrast MR angiography), 3D gadolinium-enhanced MR angiography sequences, and, more recently, time-resolved 4D gadolinium MR angiography have been shown to be highly informative in the detection of HNPGLs (Arnold et al. 2003, van den Berg et al. 2004, Neves et al. 2008), especially JPs. Fusion images between T1-weighted and the most informative images on 4D MR angiography are particularly useful for tumor delineation (Fig. 1).

CT offers several advantages over MRI (e.g., better spatial resolution and less motion artifacts) and enables better evaluation of the temporal bone extension of JP and TP. MRI provides better soft-tissue contrast than does CT and thus offers unique information for tumor delineation.

Functional imaging

To determine whether additional HNPGLs are present, anatomic imaging is inferior to PET/CT imaging. Therefore, it is currently recommended that all patients with HNPGLs are assessed by PET imaging. 18F-FDOPA, which enters cells via the L-type amino acid transporter system, was considered the most sensitive imaging modality (sensitivity >90%) in the detection of glomus tumors (King et al. 2011, Treglia et al. 2012, Gabriel et al. 2013).

Recently, PET/CT imaging using 68Ga-labeled somatostatin (SST) analogs has had excellent preliminary results (Maurice et al. 2012, Naji & Al-Nahhas 2012, Kroiss et al. 2013, 2015, Sharma et al. 2013, Janssen et al. 2015). 68Ga-based PET imaging has lower intrinsic spatial resolution and detection sensitivity compared to 18F-based PET imaging (Sanchez-Crespo 2013), although these drawbacks are partially compensated for in PGL imaging by highly elevated tumor to background uptake ratios.

68Ga-based PET imaging is rapidly evolving since it does not require a cyclotron to make the radiotracer. Previous and current studies from several centers worldwide suggest that this imaging modality will be as effective as 18F-FDOPA PET/CT or even better; it may surpass 18F-FDOPA PET in the near future also due to its easier production, availability, and distribution (Fig. 2) (J Janssen, CC Chen, D Taieb, NJ Patronas, CM Millo, KT Adams, J Nambuba, P Herscovitch, SM Sadowski, AT Fojo, I Buchmann, E Kebebew, K Pacak, unpublished observations).
68Ga-DOTATATE has recently been accorded orphan drug status by the US Food and Drug Administration, thereby increasing interest in and availability of the radiotracer. However, it should be noted that SST-based imaging may be somewhat less specific than 18F-FDOPA PET imaging in the evaluation of these tumors and could be falsely positive, mainly in metastatic lymph nodes due to various cancers, meningiomas, and inflammatory processes (Taieb et al. 2012, Hofman et al. 2015).

**Pheochromocytomas and PGLs associated with the sympathetic nervous system**

Pheochromocytoma (PHEO) develops from chromaffin cells of the adrenal medulla (also called adrenal PHEO) or extra-adrenal chromaffin (noradrenaline-producing) cells that persist postnatally in the pre- or paraaortic regions in relation to sympathetic ganglia. One of these regions is a paraganglionic complex named the organ of Zuckerkandl (OZ) that consists of a paired organ located lateral to the abdominal aorta at the level of the inferior mesenteric artery and smaller accessory paraganglia that is anterior to the aorta between the lateral organs or below the aortic bifurcation. The OZ is the largest accumulation of chromaffin cells and regresses after birth by autophagy (Schober et al. 2013). The OZ can also represent a site of origin for PGLs and occur in association with the succinate dehydrogenase complex, subunit B (SDHB), or, less frequently, subunit D (SDHD) gene mutations in more than 70% of cases (Lodish et al. 2010).

Anatomical imaging appears sufficient for localizing PHEO. Functional imaging is probably not necessary in the preoperative work-up of patients meeting the following criteria: > 40 years, no family history, small (<3.0 cm) PHEO secreting predominantly metanephrines, and negative genetic testing (Taieb et al. 2012). Functional imaging is strongly recommended for excluding metastatic disease in large adrenal tumors (> 6.0 cm), for hereditary syndromes, and in cases of suspicion of non-hypersecreting PHEO (Taieb et al. 2012, Lenders et al. 2014). In the presence of a retroperitoneal extra-adrenal non-renal mass, it is important to differentiate a PGL from other tumors or lymph node involvement, including metastases. A biopsy is not always contributory or even recommended since it can carry a high risk of hypertensive crisis and tachyarrhythmia and therefore should only be done if PGL is ruled out in any patient presenting with signs and symptoms of catecholamine excess. Specific
functional imaging studies, which are usually not performed before biochemical results are available, are very helpful in distinguishing PGL from other tumors.

**Anatomic imaging** The most common and recommended approach for localizing adrenal PHEO and sympathetic PGL is to use MR or CT. On CT, the typical imaging phenotype of a PHEO/PGL is a dense and hypervascular mass. On MR, PHEOs/PGLs have been described as enhancing masses with characteristically high signal intensity on T2-weighted imaging (found in approximately one-third of solid tumors). A wide spectrum of imaging appearances may be seen (i.e., intracellular lipid, hemorrhage, intense enhancement, calcifications, rapid contrast material washout). MR spectroscopy might also detect catecholamines (Imperiale et al. 2015) and metabolites such as succinate (Varoquaux et al. 2015).

**Functional imaging** 

$^{18}$F-FDOPA scintigraphy has a sensitivity of 77–90% and specificity of 95–100% in the detection of PHEO; its sensitivity is lower for PGLs, especially for some that are hereditary (see below). 

$^{123}$I-MIBG is as sensitive as PET imaging ($^{18}$F-FDOPA PET, $^{18}$F-FDA PET, $^{18}$F-FDG), and superior to $^{111}$In-pentetreotide SPECT (CT) in localizing nonmetastatic sporadic PHEOs (Timmers et al. 2009). Several studies demonstrated the limitations of using $^{123}$I-MIBG scintigraphy alone in the staging and restaging of hereditary and metastatic PHEOs. $^{18}$F-FDOPA PET/CT imaging has an excellent sensitivity (>90%) in metastatic PHEOs/PGLs and no interference with medications (Fig. 3). $^{18}$F-fluorodopamine ($^{18}$F-FDA) is an excellent specific functional modality for primary PHEO/PGL; however, its use for metastatic or hereditary PHEOs/PGLs is limited (Timmers et al. 2009). $^{18}$F-FDG uptake is somewhat variable across genotypes and less specific than $^{18}$F-FDOPA (Taieb et al. 2009, 2014a, Timmers et al. 2012). Several potential diagnoses should be considered in cases of highly $^{18}$F-FDG-avid adrenal masses (Fig. 4). The optimal imaging algorithm in metastatic PHEOs/PGLs is widely dependent on genetic status (see discussion below, Table 1).

**Influence of genotype on imaging phenotype**

Approximately 40% of PHEOs and PGLs carry a germline mutation in one of at least 20 genes (Martucci & Pacak 2014, Pacak & Wimalawansa 2015). These mutations are associated with transcriptome changes that are currently subdivided into two main clusters. Cluster 1 contains tumors (mostly extraadrenal) with mutations in the von Hippel-Lindau tumor suppressor ($\text{VHL}$), components of the succinate dehydrogenase complex (subunits A-D and its flavination factor SDHAF2), hypoxia-inducible factor 2-alpha, also called EPAS1 ($\text{HIF2A}$), fumarate hydratase ($\text{FH}$), prolyl hydroxylase domain-containing protein 1 ($\text{PHD1}$), and $\text{PHD2}$ genes that are associated with a pseudohypoxic signature and the activation of mainly the HIF-2alpha signaling pathway (Jochmanova et al. 2013). These tumors can be separated by their transcription profile from neoplasms (mostly PHEOs) with mutations in Ret Proto-Oncogene (RET), neurofibromin 1 (NF1), transmembrane protein 127 (TMEM127), and MYC associated factor X (MAX) mutations, which are associated with increased kinase signaling as well as...
combined HIF-1alpha and HIF-2alpha signaling pathways (Jochmanova et al. 2013, Vicha et al. 2014).

PHEOs/PGLs provide unique opportunities for discovering and proving a genotype-related imaging phenotype. However, tumor location (origin) has some influence on imaging findings since it is tightly interconnected with genotype. Furthermore, patients with hereditary syndromes these days are diagnosed early, and therefore, very small tumors may exist a priori that could be missed by nuclear imaging due to the resolution limits of PET/SPECT cameras.

In recent years, PET scanning has been growing rapidly in the localization of hereditary PHEOs/PGLs and provided some new genotype-specific imaging phenotypes of these tumors. Several studies have found that 18F-FDG PET/CT is excellent for SDHx germline mutations in comparison to other tumor types, regardless of tumor location (Timmers et al. 2012). The performance...
of $^{18}$F-FDG PET/CT is even much higher in SDHx-related metastatic PHEOs/PGLs compared to their primary counterparts or other sporadic or hereditary tumors (Fig. 5). It has been shown that $^{18}$F-FDG uptake values expressed as SUV (max or mean, ratios) enable distinction between cluster 1 and cluster 2 tumors. This finding has been shown in PHEOs (Timmers et al. 2012) and PGLs (Blanchet et al. 2014a). By using an uptake ratio, it has even been shown that models could be established for predicting PHEO/PGL genotypes (Blanchet et al. 2014a). In contrast to $^{18}$F-FDG PET/CT, the performance of $^{123}$I-MIBG scintigraphy is suboptimal (about 50% or less) in the detection of SDHx-associated metastatic PHEOs/PGLs (Fonte et al. 2012). $^{18}$F-FDOPA PET/CT is a good alternative, but well-conducted studies related to various hereditary or sporadic PHEOs/PGL (except HNPGLs) are missing. Recent studies show that, in contrast to HNPGLs, $^{18}$F-FDOPA PET/CT may miss SDHx-associated sympathetic nervous system-derived PHEOs/PGLs (Gabriel et al. 2013). These findings are currently unexplained.

Recently, Janssen et al. (2015) have demonstrated the superiority of $^{68}$Ga-DOTATATE PET/CT to other functional imaging modalities (including $^{18}$F-FDG PET/CT) in the localization of SDHB-associated metastatic PHEOS/PGLs. This is in agreement with the higher expression of SST2 in SDHx tumors compared to other subtypes (Elston et al. 2015). $^{68}$Ga-DOTATATE PET/CT may replace the currently recommended $^{18}$F-FDG PET/CT as the preferred imaging modality in the evaluation of SHDB-related metastatic PHEO/PGL (Janssen et al. 2015).

### Table 1  Stepwise imaging approaches for PHEOs/PGLs according to the localization and genotype

<table>
<thead>
<tr>
<th>Entities</th>
<th>Associated conditions</th>
<th>1st choice radiopharmaceuticals</th>
<th>2nd choice radiopharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHEO</td>
<td>MEN2 (RET), SDHx, VH1, NF1, TMEM127, MAX VH1, SDHx, Carney triad, HIF2A, PHDx SDHx, SDHAF2</td>
<td>$^{18}$F-FDOPA</td>
<td>$^{123}$I-MIBG</td>
</tr>
<tr>
<td>Extraadrenal abdominal and thoracic sympathetic PGL</td>
<td>SDHx ($B &gt; D$), FH</td>
<td>$^{18}$F-FDOPA</td>
<td>$^{68}$Ga-DOTA peptides or $^{123}$I-MIBG or $^{18}$F-FDG</td>
</tr>
<tr>
<td>Parasympathetic PGL</td>
<td></td>
<td>$^{68}$Ga-DOTA peptides (awaiting confirmation)</td>
<td>$^{18}$F-FDOPA</td>
</tr>
<tr>
<td>Metastatic PHEO/PGL</td>
<td></td>
<td>$^{68}$Ga-DOTA peptides in SDHx (awaiting confirmation)</td>
<td>$^{18}$F-FDG in SDHx</td>
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<tr>
<td></td>
<td></td>
<td>$^{18}$F-FDOPA in sporadic</td>
<td>$^{68}$Ga-DOTA peptides</td>
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**Figure 5**

Functional imaging findings in a case of extraadrenal sympathetic SDHB-related PGL. Multimodality imaging with $^{123}$I-MIBG (anterior and posterior views), SRS (three images), and $^{18}$F-FDG PET/CT. The PGL (arrow) was moderately avid for Octreoscan and quasi-negative on MIBG scan. In contrast, the tumor exhibited high $^{18}$F-FDG uptake, a finding that is typical for SDHB-tumors.
The optimal imaging algorithm is not validated in hereditary PHEOs/PGLs but most likely requires the combination of anatomical and functional imaging approaches with preferential use of $^{68}$Ga-labeled SST analogues or $^{18}$F-FDG PET/CT in cluster 1 tumors and $^{18}$F-FDOPA PET/CT in cluster 2 tumors.

**Diagnosis of malignancy**

At the present time, there are no reliable cytological, histological, immunohistochemical, molecular, or imaging criteria for determining malignancy (Gimm et al. 2012). The diagnosis of malignancy remains strictly based on the finding of metastases where paraganglial cells are not usually present, such as the lymph nodes, lung, bone, or liver. Therefore, detection of a tiny lesion may allow for the diagnosis of malignancy. To this end, imaging has a central role of ruling out metastases.

It is widely accepted that tumors with an underlying SDHB mutation are associated with a higher risk of aggressive behavior, development of metastatic disease, and ultimately death. Therefore, it is expected that the early detection and treatment of SDHB-related tumors may minimize complications related to mass effect, facilitate curative treatment, and potentially reduce the occurrence of metastases. FH-related PHEOs/PGLs seem to be the second most aggressive tumors (Castro-Vega et al. 2014, Clark et al. 2014).

**Imaging follow-up of mutation carriers**

The optimal follow-up algorithm has not yet been validated in hereditary PHEOs/PGLs but most likely requires a more frequent and complete imaging work-up than for their sporadic counterparts. MRI offers several physical advantages over CT and does not expose patients to ionizing radiation, which is critical in a patient population submitted to lifelong imaging surveillance. Scientists are waiting to find out whether, based on current data, $^{68}$Ga-DOTATATE could surpass Octreoscan in its value and utility. In SDHx-mutation carriers, follow-up should include annual biochemical screening and MRI can be delayed to 3-year intervals. Indications for PET imaging studies should be discussed on an individual basis (Lepoutre-Lussey et al. 2015). The latest improvements in PET imaging systems have increased the ability to visualize and quantify small concentrations of PET tracers (spatial resolution of 4 mm) using low-radiation doses delivered to patients. In MEN2-patients, PHEO imaging should be performed when biochemical diagnosis is established.

**Image-based treatment of PHEOs/PGLs**

**Surgery vs therapeutic radiation vs observation in HNPGLs**

In patients with HNPGLs, data suggests little to no growth over time in most cases. Observation may be considered in asymptomatic cases with a low risk of malignancy. However, provided the increasing life span, even slowly growing tumors may progress in the long term and cause delayed and irreversible complications. 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.

Complete surgical resection is curative for patients with HNPGLs. Anatomic imaging serves as the first-line modality in the locoregional staging of these tumors. MRI provides better soft tissue contrast than CT and thus offers unique information regarding tumor delineation of cervical PGLs and helps predict surgical outcome. Carotid body tumors of Shamblin classes I and II (adherent or partially surrounding the carotid vessels) are good candidates for tumor resection, with a low risk of cranial nerve palsy and vascular morbidity (Patetsios et al. 2002, Papaspyrou et al. 2012). Shamblin class III tumors (completely surrounding the carotid vessels) are at a much higher surgical risk and are typically better treated by radiation therapy.

For jugular (JP) and vagal (VP), there is a current trend toward the use of radiation therapy as a first-line treatment. By combining targeting accuracy with the steepest possible dose gradients, ablative radiosurgery should be recommended as the preferred technological choice (Taieb et al. 2014b). In these cases, radiosurgical planning is guided by anatomical and functional imaging.

Patients with multifocal HNPGLs represent a special therapeutic challenge. Subjects with bilateral HNPGLs should not undergo a one-step surgical approach since this bears the risk of bilateral cranial nerve palsies, resulting in severe disabilities. It is notable that multifocality mainly occurs in hereditary PGL syndromes. However, until most recently, some patients may exhibit multiple tumors without any mutations found in susceptibility genes. Furthermore, the genetic status is often unknown at the time of the imaging work-up. For all these reasons, we recommend a combination of anatomic and functional imaging in the evaluation of all patients with HNPGLs in order to rule out multifocality. In patients with an apparently single tumor, cranial nerve palsy may
significantly compromise additional surgery to the contralateral side. Therefore, identification of an additional tiny tumor may change the management strategy from surgery to radiosurgery or a combination of both approaches.

**Adrenal sparing surgery**

First, all known MEN2/VHL patients need to be biochemically screened, usually on an annual basis, for the presence of any newly developed unilateral or bilateral PHEOs. Once the biochemical diagnosis is established, imaging follows. CT is preferable over MR due to its excellent resolution that provides detailed anatomical locations of tumor extension within the adrenal gland and, for MEN2 patients, the number of tumors within the adrenal medulla. On the other hand, the advantage of using MR over CT is the lack of exposure to ionizing radiation, which is an important factor in hereditary cases undergoing continuous follow-up. In selected cases, functional imaging may be used in addition to anatomical imaging. A special advantage of $^{18}$F-FDOPA PET over these tracers stems from its lack of high uptake in normal adrenal glands. Based on the recent European Association of Nuclear Medicine (EANM) guidelines, $^{18}$F-FDOPA uptake should be considered as pathological only in cases of asymmetrical adrenal uptake with concordant enlarged gland or adrenal uptake more intense than the liver with concordant enlarged gland (Taieb et al. 2012). A combination of $^{18}$F-FDOPA PET/CT and CT/MR was found to be the optimal imaging strategy (Fiebrich et al. 2009, Luster et al. 2010).

Subtotal (cortical-sparing) adrenalectomy is a valid option, especially in the following hereditary PHEOs: MEN2, NF1, or VHL. In cases with bilateral PHEO, this strategy offers the advantage of potentially avoiding steroid supplementation. Therefore, it is crucial to perform regular imaging follow-up of known PHEOs in addition to biochemical testing for determining the optimal time to schedule cortical-sparing surgery. The use of biochemical testing with too long of an interval between images may compromise the technical feasibility of cortical-sparing surgery and lead to adrenalectomy. Intraoperative ultrasound might be helpful during laparoscopic partial adrenalectomy.

**Imaging-based radiation therapy planning**

Therapeutic radiation using conventionally fractionated radiotherapy or radiosurgery is an important component of the treatment of HNPGLs. Delineation of biological tumor volume of tumors may be challenging, especially after surgery. The use of PET imaging using specific tracers and optimal auto-segmentation methods might help modify the extent of biological tumor volumes (gross tumor volume) for radiotherapy planning purposes (Taieb et al. 2014b). It is expected that the use of specific radiopharmaceuticals in advanced PET/MRI integrated systems might also improve delineation of tumor residual masses (Blanchet et al. 2014b).

**Radionuclide therapy**

MIBG is a compound used for treating metastatic PHEOs/PGLs via beta-emitting particles that are released when $^{131}$I-MIBG is applied. $^{123}$I-MIBG scintigraphy is used as a companion imaging agent to assist in such a radionuclide therapy selection. PHEOs and sympathetic PGLs are most likely to benefit from $^{131}$I-MIBG than parasympathetic PGLs, the latter are often negative on $^{123}$I-MIBG scintigraphy (Kroiss et al. 2014). Extraadrenal abdominal PGL, especially those associated with SDHB mutations, could undergo dedifferentiation phenotype with loss of norepinephrine transporter (NET) or vesicular monoamine transporter (VMAT) (Fonte et al. 2012), which could then lead to treatment failures. $^{131}$I-MIBG is well tolerated and associates with disease stabilization or partial responses in more than 50% of cases and improvement of blood pressure indices, symptoms, and performance status in the majority of patients. PR or SD was achieved in more than 80% (Yoshinaga et al. 2014). Dosimetric approaches need to be developed in order to improve treatment planning in a given patient (Sudbrock et al. 2010, Sanchez-Crespo 2013).

Peptide receptor radionuclide therapy (PRRT) is an established treatment option for well-differentiated and advanced neuroendocrine tumors. To date, PRRT using $^{90}$Y/$^{177}$Lu-labelled SST analogs has been evaluated in a limited number of PHEO/PGL cases (van Essen et al. 2006, Zovato et al. 2012, Puranik et al. 2015). Response rates (mainly partial responses) have been 30–60% on average. Disease stabilization is frequent but more difficult to interpret since these tumors often exhibit a slow growing pattern. Larger studies including various hereditary and non-hereditary PHEOs/PGLs are needed in order to conclude which PHEOs/PGLs can be best treated using this therapy and whether PRRT should be used together or preferably as a ‘replacement’ to other treatment modalities.

**Future directions**

**Treatment monitoring**

Functional imaging has gained an increasing role in the evaluation of responses to systemic therapies. Beyond...
qualitative assessment of tumor response on 18F-FDG PET/CT, several studies have proposed quantitative parameters. In our opinion, evaluation of the unmetabolized 18F-FDG fraction using simplified kinetic models should be of particular interest in the in vivo assessment of responses to angiogenic agents (Barbolosi et al. 2015). 18F-FDOPA PET/CT might also provide valuable information in the evaluation of mTOR inhibitors due to the interconnection between LAT1 and mTOR pathways (Ganapathy et al. 2009).

Radionuclide therapy

Promising results have been obtained with Ultratrace Iobenguane I-131 (AZEDRA) in patients with malignant relapsed/refractory PHEOs/PGLs (Jimenez et al. 2015).

In an attempt to improve results, cytostatic agents should be also combined with internal targeted radiotherapy in a sequential manner. However, some tumors are not positive on 123I-MIBG scintigraphy. Manipulation of NETs using HDAC inhibitors or other drugs need to be further evaluated (Martiniova et al. 2011). These approaches, in conjunction with radiosensitizers, might increase the number of patients eligible for radionuclide therapy and enhance antitumoral effect by elevating radiation doses delivered to the tumors. Redifferentiation approaches have been developed for iodine-refractory thyroid cancer, with promising initial results (Ho et al. 2013). 177Lu-DOTATATE will also be rapidly implemented into the therapeutic arsenal for PHEOs/PGLs. This option might be introduced as adjuvant treatment after debulking surgery or in the ablation of small lesions or those located in the most inaccessible anatomical areas. 68Ga-DOTATATE can be used as a companion agent in selecting good candidates for this therapy. However, its short half-life makes 68Ga questionable for pre-therapeutic internal dosimetry.

Probes

PET imaging has been widely developed in the evaluation of PHEO/PGL patients. Intraoperative localization of PET-positive lesions can be facilitated using a handheld PET probe and would be of particular interest for reoperative surgery of recurrent PHEOs/PGLs (Das et al. 2014).

Gene-targeting and nanobodies-based nuclear imaging and theranostics

Molecular imaging also enables for the visualization of gene expression in genetically modified cells that contain reporter systems encoding for an enzyme, a receptor, or a transporter (reporter gene imaging). Some of molecular imaging’s ultimate goals are to provide direct information on endogenous gene regulation, mRNA stabilization, and specific protein–protein interactions. Radiolabeled oligonucleotides can be useful for targeting mRNA, thereby serving as non-invasive tools for the detection of endogenous gene expression in vivo (antisense imaging). The success of antisense imaging relies heavily on overcoming the barriers for its targeted delivery in vivo. This goal could be achieved by the use of nanovectors for mRNA delivering. The development of nanotechnology-based antisense imaging could represent new tools for the identification of more specific imaging phenotypes tightly linked to tumor genotypes. These nanoparticles may also code deliver imaging agents and therapeutic drugs.

Nanobodies also have the future potential of serving as diagnostic and theranostic tools in oncology (D’Huyvetter et al. 2014). Several approaches have already been developed, such as radiolabeled nanobodies against VEGFR2 and CAIX, and could be evaluated in PHEOs/PGLs.

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