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Current and future trends in the anatomic and functional imaging of head and neck paragangliomas

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Abstract

Head and neck paragangliomas (HNPGLs) account for approximately 3% of all paragangliomas (PGLs). Most often, HNPGLs are benign, non-secreting, and slowly progressing. The initial physical examination and biochemical diagnosis usually adds very little to the proper diagnosis of these tumors and therefore, radiologists and nuclear medicine physicians play the pivotal role in providing the initial diagnosis, the locoregional staging, and the plan for detecting potential multicentric or metastatic lesions. Based on several current studies, the most accurate use of HNPGL-specific initial and subsequent imaging modalities must be guided by the knowledge of genetics and the specifically measured biochemical profile of these tumors for the proper management of these patients. Thus, this short review article presents the application of the most up-to-date anatomic and functional imaging approaches to HNPGLs tightly linked to the clinical management of these patients. Based on the most recent studies, 18F-FDOPA PET/CT has been shown to be a useful addition to anatomic imaging in the preoperative localization and molecular assessment of HNPGLs. It is estimated that the frequency of metabolically active PGLs on 18F-FDOPA PET/CT in this region is higher than 90%. 18F-FDG PET/CT should be reserved for patients with hereditary PGL syndromes. Imaging of somatostatin receptors using Octreoscan or 68Ga-labeled somatostatin analogs plays an important role for selecting patients for targeted radiation therapy.

This review also concludes that it is expected that in the near future, these patients will indeed benefit from new diagnostic approaches based on the identification of new targets by molecular profiling studies that will result in the development of novel PGL specific radiopharmaceuticals.

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Keywords

Positron emission tomography; computed tomography; paraganglioma; radiopharmaceuticals; genetics; head and neck

Definition and anatomy of HNPGLs

Head and neck paragangliomas (HNPGLs) are neural crest-derived neuroendocrine neoplasms arising from head and neck paraganglia that are closely aligned along the parasympathetic nervous system, some of which act as chemoreceptors. HNPGLs account for about 0.6% of all neoplasms in the head and neck region and approximately 3% of all PGLs (1). They are widely distributed, with a predilection for the following sites: the jugular foramen (glomus jugulare PGL), cochlear promontory (glomus tympanicum PGL), prestyloid pharyngeal space (vagal PGL), carotid bifurcation (carotid body PGL), or other unusual or exceptional locations (e.g., larynx, thyroid, sinonasal region, nasopharynx, orbit, tongue). Since HNPGLs are usually non-secreting tumors, they are most often discovered on imaging studies carried out due to neck swelling or by symptoms of compression or infiltration of the adjacent head and neck structures (e.g., otologic symptoms, dysphagia, cranial nerve palsies).

Clinical and genetic update on HNPGLs

Although most HNPGLs arise sporadically, PGL susceptibility genes have been identified in approximately one-third of cases with a single, apparently sporadic tumor, and in more than 90% of patients with multifocal tumors (2, 3). Hereditary HNPGLs are most frequently associated with germline mutations in one of the succinate dehydrogenase (SDH) subunits genes (SDHB/D and rarely SDHC/A) or its flavination factor SDHAF2 (4). The spectrum of clinical manifestations in patients with von Hippel-Lindau (VHL) and recently discovered transmembrane protein 127 (TMEM127) mutations has also been extended to rarely include HNPGLs (5, 6). The inheritance pattern of the SDHB and SDHC genes is autosomal dominant, whereas for SDHD and SDHAF2 genes, there is virtually an exclusive autosomal dominant paternal transmission of the disease (7). Major predictors for hereditary HNPGLs are family history of PGL, although less frequently available due to a low penetrance of these tumors, previous history of adrenal or extra-adrenal PGL, and multifocality or characteristic syndromic presentation (2, 8). In addition, the existence of other tumor types (e.g., renal cell carcinoma (9), gastrointestinal stromal tumor and/or pulmonary chondroma in Carney–Stratakis dyad or triad (10), pituitary adenoma (11)) or a dopaminergic biochemical phenotype based on the measurement of a new plasma biomarker, the dopamine metabolite 3-methoxytyramine, can be indicative of SDH-related PGLs (12). Of all the known genetic mutations, mutations in SDHD are currently the leading cause of HNPGLs, followed by SDHB mutations (3, 13). Furthermore, it should be noted that multiple PGLs at a very young age found in several family members are often related to SDAF2 mutations (14). Moreover, PGLs with an underlying SDHB mutations are associated with a higher risk of metastatic and perhaps locally aggressive behavior (15), which may also apply to HNPGLs, although properly designed studies are missing.

Anatomic imaging as the first line imaging in the localization of HNPGLs

At present, anatomic imaging remains the first-line modality in the localization of these tumors, since practically no surgery would be carried out without a precise delineation of these tumors. Multidetector computed tomography (MDCT) and magnetic resonance (MR) are both considered gold standards for HNPGL imaging, although each modality has advantages and disadvantages (**Figures 1-7**). Current CT technology offers several physical

advantages over MR (e.g., better spatial resolution and less motion artifact) and enables better evaluation of the temporal bone extension of glomus jugulare and glomus tympanicum PGLs (Figures 2-4, 6, 7). However, MR provides better soft tissue contrast than CT and thus offers unique diagnostic and prognostic information as well as not using ionizing radiation (Table 1). HNPGs demonstrate marked enhancement of intra-tumoral vessels following contrast administration on CT and 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. MR angiography also demonstrates intra-tumoral arterial vessels (16-20). 3D time-of-flight (11 minutes at 3 Tesla for a 10 cm field of exploration) and 3D gadolinium (58 seconds for a 30 cm field of exploration) sequences were shown to be highly informative, with sensitivities and specificities of 90% and 94% (17) and 100% and 94% (18), respectively. There is a current trend to use time-resolved 4D gadolinium MR angiography (TRICKS, 5 seconds for a 22 cm field of exploration) (20). TRICKS enables evaluation of both intratumoral vessels (early arterial phase) and tumor perfusion, including capillary permeability. Compressive sensing is currently being developed for reconstruction of images and permits acceleration factors approaching 1000 (21). In our experience, fusion images between 3D volumetric interpolated fat-saturated (FATSAT) T1-weighted (VIBE) and 4D-MR angiography are particularly informative (Figures 1-3, 7). Ultrasound is a good non-invasive method, but it is limited to the evaluation of neck PGLs (carotid body and large vagal PGLs) and is mostly performed only when radiation exposure must be limited (e.g., pregnancy, previous excessive exposure to radiation) or due to contrast allergy. Thus, localization of HNPGs is often easily done by radiological imaging, but these techniques often lack specificity. For example, 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. Diffusion-weighted imaging (DWI), which is dependent on tissue cellularity, may be useful in preoperative characterization and prognosis assessment of PGL, but further evaluation is needed (22). Positron emission tomography (PET)/MR using an integrated system with simultaneous acquisition of both techniques also holds promise for HNPG, most likely for anatomical sites after a previous operation (e.g., recurrence). Angiography is usually not needed for localization of these tumors and when used, is most often performed for pre-operative vascular mapping followed by endovascular embolization in order to minimize blood loss intraoperatively. Furthermore, in some situations it is also required to assess the vascular supply of a HNPG to plan an appropriate surgical intervention.

Current functional imaging in the localization of HNPGs

Radionuclide imaging techniques now play a crucial and unavoidable role in the evaluation of HNPGs. This is due to the increasing availability of radiopharmaceuticals that have been developed to target receptors or metabolic pathways specific to these tumors, essentially and uniquely performing so-called in vivo histology. Traditionally, the most successful strategy has been to target the cell membrane norepinephrine transporter (NET) and intracellular vesicular monoamine transporter (VMAT) systems, used for cellular entry and catecholamine storage, with $^{123}\text{I}/^{131}\text{I}$ -metaiodobenzylguanidine ($^{123}\text{I}/^{131}\text{I}$ -MIBG). ^{123}I -MIBG scintigraphy is highly specific for chromaffin-derived tumors. Its sensitivity ranges from 90-100% in sporadic PHEOs, but significantly decreases in SDHx-related tumors (23), especially in HNPGs (24).

More recently, somatostatin receptor scintigraphy using ^{111}In -DTPA-pentetreotide (also called Octreoscan) has been used to localize PGLs, since they overexpress somatostatin

receptors, especially subtype 2 (SST2). Several excellent studies have demonstrated the superiority of Octreoscan for HNPGLs compared to $^{123}\text{I}/^{131}\text{I}$ -MIBG, with sensitivities of 89-100% and 18-50%, respectively (25-30). However, the sensitivity of this imaging modality needs to be revised downwards because some lesions can be only a few millimeters in size and therefore are not detectable by even the best available cameras (sensitivity 75% with SPECT) (Table 1) (31). The recently introduced hybrid SPECT/CT cameras have increased diagnostic confidence in image interpretation and enhanced sensitivity, but practical constraints such as long imaging times remain important limitations. Based on these studies, ^{123}I -MIBG has been practically abandoned in the evaluation of these tumors, except in situations where targeted radiotherapy can be planned using ^{131}I -MIBG. In contrast, the presence of SST receptors has led to the further evaluation of somatostatin peptide analogs in the localization and subsequent treatment of these tumors. More recently, PET/CT imaging has been growing rapidly in the imaging of these tumors, paralleled by great efforts towards the development of PGL-specific radiopharmaceuticals. PET imaging with ^{68}Ga -labeled somatostatin analogs (^{68}Ga]SSTa) has been introduced as an alternative to Octreoscan (32-35). Currently, three DOTA-coupled peptides are available: DOTATOC (Tyr3-octreotide), DOTATATE (Tyr3-octreotate), and DOTANOC (Nal3-octreotide); all have an excellent affinity mainly for SST2 receptors (IC₅₀: 2.5 nM; 0.2 nM; and 1.9 nM, respectively) (36-38). DOTANOC also binds specifically to SST3, SST4, and SST5 receptors, but the expression of SST3 and SST4 is absent in PGLs and SST5 is strongly expressed in only 5% of cases (Table 2).

Two other radiopharmaceuticals have been developed to investigate the catecholaminergic metabolism system: ^{11}C -hydroxyephedrine (^{11}C -HED) and ^{18}F -fluorodopamine (^{18}F -FDA). They were first developed to investigate the sympathetic innervation of the myocardium. ^{11}C -HED has shown excellent results in the setting of PHEOs (39) but has limited use because of the very short half-life of ^{11}C (20 min). Because of this major drawback, ^{18}F -FDA was first developed and initially evaluated in PGLs of sympathetic origin with excellent results. However, subsequent studies found this radiopharmaceutical to be suboptimal for HNPGLs (46%) (24), and its use in the localization of these tumors should be limited and perhaps abandoned.

Because of initial disappointing results with ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT (40), its evaluation in PGL has been delayed until several recent excellent and large studies evaluating various sympathetic PGLs (overall sensitivity 80%) (41-43). The latest SDHx discoveries in the pathogenesis of these tumors have suggested a role for the specific use of ^{18}F -FDG PET in certain tumors, since it has been shown that PGL-specific imaging phenotypes might be different across different genotypes. ^{18}F -FDG PET has been found to be highly sensitive for sympathetic SDHB-related PGLs (42, 43). Less data is available for patients with HNPGLs (24), which are parasympathetic and do not follow the rule of ^{18}F -FDG PET/CT superiority over other imaging modalities in the evaluation of SDHB-related PGLs. Therefore, ^{18}F -FDG PET is not indicated in HNPGLs as the first-line imaging modality (Figures 1, 2, 6, 7).

^{18}F -fluorodopa (^{18}F -FDOPA), which was initially developed to investigate dopaminergic neurotransmission, is taken up through a neutral amino acid transporter (LAT1/4F2hc complex) and decarboxylated into ^{18}F -FDA by aromatic L-amino acid decarboxylase (AADC). Hoegerle et al. were the first to uniquely demonstrate the utility of ^{18}F -FDOPA PET to localize PGLs (44). Hoegerle et al. found 100% sensitivity in a small series of 10 patients (15 tumors) and demonstrated that the high signal-to-noise uptake ratio enabled the detection of sub-centimetric lesions (45). Subsequent studies compared ^{18}F -FDOPA to other imaging modalities and radiopharmaceuticals across different PGL locations and genotypes (46). ^{18}F -FDOPA PET/CT was found to be a sensitive (80-90% for abdominal PGLs and

>95% for HNPGLs) and specific (95-100%) imaging modality for the detection and staging of non-metastatic PGLs (24, 46-49) (Figures 1-7). ^{18}F -FDOPA PET was also found to be superior to Octreoscan (24, 47) in the detection of HNPGLs and to be excellent for both SDHx (24) and non-SDHx (48) PGLs. In the largest series, 116 PHEO/PGL patients from two academic endocrine tumour centers were investigated with ^{18}F -FDOPA PET or PET/CT imaging. The detection rate was higher for parasympathetic PGLs (98.2%) than for sympathetic PGLs and not affected by the genetic status of patients. This study and the previous ones (comprising a total sample size of about 200 HNPGLs from 6 studies) suggest without any reservation that ^{18}F -FDOPA PET/CT is currently the first-line imaging modality in the localization of HNPGLs, regardless of genetic background (24, 42, 47, 48, 50-53).

The optimal timing for acquisition remains to be evaluated, as well as the use of oral premedication with carbidopa, an inhibitor of AADC (54, 55).

However, ^{18}F -FDOPA is not routinely available at most imaging centers worldwide. Furthermore, the current leading role of ^{18}F -FDOPA PET/CT in the evaluation of HNPGL will need to be compared to newly introduced and promising agents such as ^{68}Ga -SST receptor analogs. In the absence of ^{18}F -FDOPA or ^{68}Ga -SST receptor analogs, SRS with ^{111}In -pentetreotide SPECT (/CT) acquisition may be used as the first-line evaluation. In patients with multifocal disease, elevated metanephrines, or SDHx mutations, additional investigations are required to fully evaluate the extent of the disease.

Proposed imaging algorithm in the localization of HNPGLs and their management

Based on the currently available imaging techniques in the diagnosis and staging of PGLs, we propose the following approach to a patient with HNPGL:

1. The first step is to confirm the diagnosis of HNPGL and to determine whether solitary or multifocal tumors are present. For this purpose the initial information provided by MRI is superior to CT.
2. The next step is to further characterize these tumors, first to confirm that these tumors are indeed PGLs and second to determine whether additional tumors are present, since MRI is inferior to functional imaging using ^{18}F -FDOPA PET/CT. Based on the most recent studies, both SDHx and non-SDHx PGLs are well detected by ^{18}F -FDOPA PET/CT.
3. The third step is to fully evaluate the temporal bone extension of tympanic and jugular HNPGLs for surgical decision-making based on MR imaging.
4. The last step is to determine patients who are not candidates for surgery, which in our experience is most successfully done by ^{18}F -FDOPA PET/CT, which has the highest sensitivity, and thus select patients who would benefit from radiotherapy. For external beam radiation therapy, there is no need to perform additional imaging techniques. For targeted radiation therapy, the use of Octreoscan or PET imaging using ^{68}Ga -labeled somatostatin analogs should be used for selecting potential candidates for ^{177}Lu -DOTA-Octreotate (Lutathera®). Since $^{123/131}\text{I}$ -MIBG is much less sensitive for HNPGLs than radiolabeled somatostatin peptide analogs, we suggest that the use of ^{131}I -MIBG should be limited and perhaps abandoned.

Accurately localizing HNPGLs plays a critical role in the management of patients with these tumors, especially in determining the feasibility of surgery.

Surgical removal of HNPGLs remains the primary treatment of choice but can be associated with some morbidity. The current aim of surgery is two-fold: oncologic and functional. The functional risk of radical resection needs to be balanced with the usual slow growth of most of these tumors. Therefore, some advocate that tumors less than 2 cm in size could be followed rather than risk surgical removal. On the other hand, curative surgery after early detection of a HNPGL is often expected and even demanded by patients in order to avoid subsequent complications related to mass effect and its related neurological complications, and thus must be considered. In these situations, surgery is usually performed if complete tumor excision is medically and surgically feasible, particularly in younger patients, in the case of large tumors that soon may or already present with cranial nerve deficits, and in rare catecholamine-secreting HNPGL to prevent cardiovascular consequences. By classifying tumor extension according to different classifications (i.e., Fisch and Mattox's, Glasscock and Jackson's, Netterville's, Shamblin's), radiological imaging can help predict surgical outcome (56-59). For example, for Shamblin II (partial surrounding of internal and external carotid arteries) and III (complete surrounding of the carotid vessels) carotid body PGLs, complete resection is challenging and may require temporary interruption of the cerebral circulation and major vessel reconstruction (Figure 1).

The detection of multifocality as well as knowledge of the genetic status of these tumors also has an important impact on the decision-making process, especially whether surgery should be an option or not (Figure 6 and 7). Current recommendations are to treat bilateral cervical PGLs sequentially due to the morbidity risk (60). The choice of which side to operate on first is based on the location, tumor size, and preoperative functional status of the facial and lower cranial nerves.

In high-risk situations where surgical options are limited or suboptimal, alternatives include watchful waiting or radiotherapy. New fractionated radiotherapy modalities (i.e., conformal radiotherapy, 3D conformal intensity-modulated radiotherapy, conventional stereotactic radiosurgery) allow escalated radiation dose delivery to tumors and better preservation of surrounding normal tissues at risk. Single and hypofractionated stereotactic radiotherapy using gamma-knife radiosurgery and Cyberknife®, respectively, also appear very promising, with excellent tumor control and a low morbidity rate (61-64). Cyberknife® also offers the opportunity to treat large tumors with extracranial sites, including moving tumor targets by using real-time tracking and automatic correction. Long-term results are not yet available to definitively evaluate the outcomes (i.e., the therapeutic efficiency or toxicity) of these different approaches. Intensity-modulated proton therapy also enables excellent target coverage, homogeneity within the planned target volume, and sparing of the organs at risk. However, its clinical relevance in the setting of HNPGLs has not yet been evaluated. Radiotherapy planning can also benefit from ¹⁸F-FDOPA PET/CT and other imaging, which might be useful to help delineate the biologically active tumor volume and to distinguish between viable tumor and non-specific changes due to previous treatments.

Another approach is to target isolated tumor cells directly with beta emitters such as ¹³¹I-MIBG or ¹⁷⁷Lu and/or ⁹⁰Y radiolabeled somatostatin analogs. The role of ¹²³I-MIBG should be limited to evaluating patients in whom tumors cannot be surgically removed to see if they are potential candidates for ¹³¹I-MIBG therapy.

In summary, successful management of patients requires an interdisciplinary team approach. Precise identification of the clinical context and genetic status of patients enables a personalized use of functional imaging modalities.

Future directions

Future studies are also needed to evaluate the performance of ^{18}F -FDOPA PET/CT and other radiopharmaceuticals in the detection and characterization of VHL/SDHAF2/TMEM-127-related HNPGLs, detection of recurrent HNPGLs, the ability of imaging studies to predict metastatic behavior based on specific cellular characteristics, and the role of quantification in the use of various radiopharmaceuticals in the evaluation of treatment response.

The calculation of more reliable quantitative parameters besides the standardized uptake value (SUV) could be of particular value in the in vivo assessment of these tumors at the molecular level.

Excellent results from molecular profiling studies now provide important and promising information in the identification of new therapeutic and imaging targets, particularly for various types of PGLs (65, 66). New radiopharmaceuticals that are targeted to angiogenesis (radiolabeled RGD peptides), apoptosis, hypoxia, and glycolysis are of particular interest in the characterization of these tumors (67). SDH-related PGLs are known to result in the dysfunction and destabilization of the SDH complex (mitochondrial complex II) and the preferential activation of the HIF-2 signaling pathway. Currently, there is no radiopharmaceutical to assess the degree of mutation-specific mitochondrial dysfunction or the degree of HIF-2 stabilization. It is expected that these radiopharmaceuticals will be introduced in the future, after specific HIF-2 inhibitors or mitochondrial-specific targeted compounds are introduced (68).

Nanomedicine applications have recently gathered great attention in the field of imaging. It is expected that synthesized multifunctional and multivalency agents may increase tracer delivery, enable co-delivery of therapeutic or diagnostic agents, and enable the targeting of intracellular proteins (69).

The diagnosis of malignancy, which remains challenging, may also benefit from these new imaging approaches. Malignancy, which may occur in about 5% of HNPGLs, is often discovered several years after the resection of the primary tumor when locoregional and/or distant metastases are discovered. Many radiopharmaceuticals are expected to have the potential to serve as predictive biomarker classifiers.

As for other cancers, functional imaging including PET must and will rapidly shift towards tumor specific characterization tightly linked to appropriate therapy selections and individualized medicine, resulting in more optimal treatment with cost-effective outcomes.

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Figure 1. Typical carotid body paraganglioma

T2-weighted 3D imaging with different flip angle evolutions in curve (A), axial (B), and coronal reconstructions (E); 3D volumetric interpolated fat-saturated (FATSAT) T1-weighted (VIBE) in curve (C), axial (D), and coronal reconstructions (F); ^{18}F -FDG PET/CT (maximal intensity projection (MIP)) (G) and ^{18}F -FDOPA PET/CT (MIP) (H).

MRI shows a “lyre sign” related to a 5-centimeter left carotid body PGL (red arrowheads) arising from the carotid bifurcation, splaying the internal carotid artery (ICE) (A-E, white arrows) and external carotid artery (ECA) (A-D, white arrowheads). Note small central necrosis in the tumor (E, F, red asterisk) and the lack of flow voids due to high temporal resolution of 3D sequences, especially for high-field MRI. 3D reconstructions demonstrate 360° carotid invasion along the common carotid, ICA, and ECA. ^{18}F -FDG PET/CT and ^{18}F -FDOPA PET/CT show a single highly-avid carotid body PGL.

Figure 2. Tympanic paraganglioma extending into the petrous apex

Axial 3D volumetric interpolated fat-saturated (FATSAT) T1-weighted (VIBE) (A), early arterial 4D Dynamic MR Angiography (MRA) (B), FATSAT T1-weighted/4D-MRA 3D fusion image (C), T2-weighted 3D imaging with different flip angle evolutions (D), CT reconstruction with a bone algorithm in the axial plane (E) and coronal oblique plane (F), axial ^{18}F -FDG PET (G), axial and coronal ^{18}F -FDOPA PET (H,I).

Tympanic PGL (red arrowheads) spreading along Jacobson's nerve canal (A, C-F, white arrows) deeply into the petrous apex along the cochlear aqueduct (white arrowheads, A-C, E). The CT shows integrity of the promontory and round window (F, black arrowheads) before surgical procedure. Note the early enhancement of the superior petrosal sinus suggesting tumor invasion (A-C, asterisk). ^{18}F -FDOPA PET shows a highly avid tympanic PGL with extension in the anteromedial plane. The tumour was barely visible on ^{18}F -FDG PET.

Figure 3. Tympanic paraganglioma in a rare attical location

Coronal SE T2-weighted (A), non-EPI-b1000-DWI (B), early arterial 4D Dynamic MR Angiography (MRA) (C), fat-saturated (FATSAT) T1-weighted/4D-MRA fusion image (D), CT reconstructions with a bone algorithm (E, F, G), coronal ^{18}F -FDOPA PET (H), axial ^{18}F -FDOPA PET (I), and axial ^{18}F -FDOPA PET/CT fusion image (J).

Chronic otitis media with full field tympanic cavity (A, white arrow) associated with an 8 mm inflammatory polyp in the external auditory canal (E, F, red asterisk). Absence of cholestatoma on non-EPI-b1000-DWI (B). MRI shows a 7 mm attic paraganglioma, located in the superior and medial side of the uncudo-malleal joint, with a typical hyper-vascularization pattern (C, D, red arrowhead). CT reconstructions were useful in the preoperative evaluation of the tegmen tympani's integrity (G, white arrowhead), the facial nerve canal (E: white arrows, F: black arrow), and the otic capsule (E, arrow heads). The tumor was highly avid for ^{18}F -FDOPA.

Figure 4. Residual tympanic PGL after surgery

Axial SE T1-weighted (A), early arterial contrast-enhanced T1-weighted (B), early venous contrast-enhanced T1-weighted (C) and T2-weighted (D), CT scan with a bone algorithm (E), time-intensity curve on dynamic contrast-enhanced MRI (F), axial ^{18}F -FDOPA PET (G), axial ^{18}F -FDOPA PET/CT fusion image (H), coronal ^{18}F -FDOPA PET/CT fusion image (I).

Previous canal wall up tympanomastoidectomy (A-E, asterisk). Residual tympanic PGL (A-E, red arrowheads) located in the petrous apex, posteriorly to the carotid artery (white arrowheads) and lateral to the cochlear aqueduct (arrows). The time-intensity curve shows arterial enhancement of the PGL and enables precise delineation of the lesion prior to sigmoid sinus and nasopharyngeal mucosa enhancements. ^{18}F -FDOPA PET was positive (red arrowheads).

Figure 5. Post-therapeutic evaluation of a jugular PGL

Axial reconstructions at the level of the petrous apex (A-F) and basilar process of the occipital bone (G-I), T2-weighted (A), inverted b1000 DWI MRI (B), T2-weighted/MRI-inverted b1000 DWI MRI fusion images (C), Dixon FATSAT (3D) T1-weighted 3D (D), axial ^{18}F -FDOPA PET (E, H), axial ^{18}F -FDOPA PET/MRI (T2-weighted) fusion images (F, I).

Post-operative status with canal wall down tympano-mastoidectomy (A, D, white arrows). Post-operative cholesteatoma in the tympanic cavity with a typical hypersignal on T2-weighted and b1000 DWI MRI (A, B, C, arrowheads). Double recurrent ^{18}F -FDOPA-positive PGL: the first involving the edge of the right petrous apex (D-F, red arrowheads) and the second involving the basilar process of the occipital bone, retro-pharyngeal, and para-pharyngeal spaces (G-I, red arrows). (Image kindly provided by Prof. Minerva Becker and Prof. Osman Ratib, University Hospital of Geneva, Switzerland).

Figure 6. Multifocal PGL with vagal and jugular locations

Axial SE T2-weighted (A), T1-weighted (B), FATSAT (3D) T1-weighted (C), CT angiogram in the axial (D) and sagittal planes (E), CT bone reconstruction in the axial plane (F), sagittal ^{18}F -FDG (G) and ^{18}F -FDOPA PET (H), axial ^{18}F -FDOPA PET/CT fusion image.

Vagal PGL (red arrow) arising from the posterior parapharyngeal space, splaying anteriorly the internal carotid artery (white arrow), with typical flow voids and massive enhancement. Imaging reveals an additional jugular PGL (red arrowhead) with typical wet sugar bone erosion of the jugular foramen. Both lesions were positive for ^{18}F -FDG and ^{18}F -FDOPA.

Figure 7. Multifocal and recurrent SDHD-related extra-adrenal PGLs

Coronal 3D volumetric interpolated fat-saturated (FATSAT) T1-weighted (VIBE) (A), early arterial 4D Dynamic MR Angiography (B), FATSAT T1-weighted/4D-MRA 3D fusion image (C), coronal CT bone reconstruction of the right (D) and axial oblique CT bone reconstruction of the left ear (E), ^{18}F -FDG PET (MIP) (F), and ^{18}F -FDOPA PET (MIP) (G). MRI with 4D Dynamic MR angiography shows bilateral jugular PGL (red arrows), spreading in the tympanic cavity on the left side, and a right vagal PGL (red arrowheads). CT shows bilateral enlargement of the jugular foramens and sugar bone erosions (D, E). The left tegmen tympani and the anterior wall of the attic are widely eroded by jugulo-tympanic PGL (A, E, white arrowhead). The tumor mass effect is responsible for a complete prosthetic luxation (E, white arrow), explaining the recurrent left conductive hearing loss. ^{18}F -FDG and ^{18}F -FDOPA PE/CT also reveal a mediastinal parasympathetic PGL (F, G, black arrowheads). In comparison to ^{18}F -FDG PET/CT, ^{18}F -FDOPA PET missed an abdominal paraaortic PGL (F, black arrow) and detected one more HNPG (left vagal PGL,

G; red arrowhead). False negative sympathetic PGL on ^{18}F -FDOPA PET is not uncommon in SDHx-related PGL syndromes.

Table 1

Expression of somatostatin receptor subtypes in PGL and respective affinity profiles of radiolabeled somatostatin agonists.

	SST1	SST2	SST3	SST4	SST5
% of PGLs with strong overexpression of SSTs	20%	80%	–	–	5%
Native SS-28	+++	+++	+++	+++	+++
Octreotide (OC)	–	+++	+	–	++
[111In]-DTPA-OC (Octreoscan)	–	++	+	–	+
[68Ga]-DOTA-TOC	–	++++	+/-	–	++
[68Ga]-DOTA-TATE	–	++++	–	+	+/-
[111In]-DOTA-NOC	–	++++	++	+	+++

SS-28: Native somatostatin (SRIF₂₈)

Affinity (IC₅₀, nM): <5++++, 5 – <40 = +++, 40 – <100 = ++, 100 – <300 = +, 300–<1000 = +/-, 1000 = –.

Table 2

Comparison of different imaging techniques.

	Sensitivity	Specificity	Locoregional staging	Mean estimated effective dose equivalent
MDCT (pre-contrast and angio-CT)	80-90%	90%	+++ (>MRI for bony structures)	3 mSv for unenhanced CT and 5 mSv for CT angiogram
MRI	80-90%	90%	+++ (>CT for soft tissue)	None
Octreoscan	65-75%	90-95%	+	0.06 mSv/MBq for Octreoscan and 1 mSv for low-dose CT
PET/CT - ^{18}F -FDOPA	90-100%	>95%	+ / ++	0.025 mSv/MBq for ^{18}F -FDOPA and 3 mSv for low-dose CT
^{123}I -MIBG	30-40%	>95%	+	0.013 mSv/MBq for ^{123}I -MIBG and 1 mSv for low-dose CT
PET/CT - ^{18}F -FDG	80%	80-90%	+	0.019 mSv/MBq for ^{18}F -FDG and 3 mSv for low-dose CT
PET/CT - ^{18}F -FDA	45-55%	>95%	+	0.0068 mSv/MBq for ^{18}F -FDA and 3 mSv for low-dose CT