Endocrine (2019) 64:14–30
https://doi.org/10.1007/s12020-019-01895-z

REVIEW

Check for updates

Novel PET tracers: added value for endocrine disorders

Sébastien Bergeret[1] · Judith Charbit[1] · Catherine Ansquer[2,3] · Géraldine Bera[1,4] · Philippe Chanson[5,6] · Charlotte Lussey-Lepoutre[1,7]

Received: 13 January 2019 / Accepted: 5 March 2019 / Published online: 14 March 2019

Summary

Nuclear medicine has been implicated in the diagnosis and treatment of endocrine disorders for several decades. With recent development of PET tracers, functional imaging now plays a major role in endocrine tumors enabling with high performance to their localization, characterization, and staging. Besides ^{18}F-FDG, which may be used in the management and follow-up of endocrine tumors, new tracers have emerged, such as ^{18}F-DOPA for neuroendocrine tumors (NETs) (medullary thyroid carcinoma, pheochromocytomas and paragangliomas and well-differentiated NETs originating from the midgut) and ^{18}F-Choline in the field of primary hyperparathyroidism. Moreover, some peptides such as somatostatin analogs can also be used for peptide receptor radionuclide therapy. In this context, Gallium-68 labeled somatostatin analogs (^{68}Ga-SSA) can help to tailor therapeutic choices and follow the response to treatment in the so-called "theranostic" approach. This review emphasizes the usefulness of these three novel PET tracers (^{18}F-Choline, ^{18}F-FDOPA, and ^{68}Ga-SSA) for primary hyperparathyroidism and neuroendocrine tumors.

Keywords PET/CT · Neuroendocrine tumors · Primary hyperparathyroidism · 18F-Choline · 18F-FDOPA · Gallium-68 · Somatostatin · 18F-FDG

Introduction

For several decades, nuclear medicine has gained an important place in the diagnosis of endocrine disorders, particularly in the field of neuroendocrine tumors (NETs). In the last 15 years, the development of positron emission tomography combined with computerized tomography (PET/CT) has stimulated research in this field, resulting in the development of novel radioactive tracers, some of which are now widely used in endocrinology (Table 1). In this review, we discuss the role of three novel PET tracers (^{18}F-Choline, ^{18}F-FDOPA, and ^{68}Ga-labeled somatostatin analogs (^{68}Ga-SSA)) as diagnostic tools in the diagnosis of endocrine tumors, in addition to ^{18}F-FDG, the most commonly used PET tracer.

Evolution of nuclear medicine imaging techniques

The concept of functional imaging in nuclear medicine consists the direct exploration of metabolic systems using radioactive tracers with a specific in vivo molecular target. Conventional planar scintigraphy was the first modality

These authors contributed equally: Sébastien Bergeret, Judith Charbit

✉ Charlotte Lussey-Lepoutre
charlotte.lussey@inserm.fr

1 Sorbonne University, Nuclear Medicine Department, Pitié-Salpêtrière Hospital, 47-83 Bd de l'Hôpital, 75013 Paris, France

2 Nuclear Medicine Department, CHU-Hôtel Dieu, 1 Place Alexis Ricordeau, 44093 Nantes Cedex1, France

3 CIRCINA INSERM, Angers University, 8 quai Moncousu, 44000 Nantes, France

4 INSERM U1146, Laboratoire d'imagerie Biomedicale (LIB), Sorbonne University, Paris, France

5 Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Service d'Endocrinologie et des Maladies de la Reproduction, Centre de Référence des Maladies Rares de l'Hypophyse, Le Kremlin Bicêtre F-94275, France

6 INSERM UMR S1185, Fac Med Paris Sud, Univ Paris-Sud, Université Paris-Saclay, Le Kremlin-Bicêtre F-94276, France

7 INSERM U970, Georges Pompidou European Hospital Cardiovascular Research Center, 56 rue Leblanc, 75015 Paris, France

Table 1 Main indications of PET tracers used for NET evaluation

	MTC	PPGL	GEP NETs			Lung NETs
			Foregut	Midgut	Unknown	
^{18}F-FDopa	++ (residual disease with CT > 150 pg/ml)	- Head and neck PGL - PGL with *SDHD* mutations - Pheochromocytomas	+/–	+++	+	+/–
^{68}Ga-SSA	+/–	- Metastatic PPGL - Head and neck PPGL - PPGL with *SDHB* mutations	+++	+++	++	+++ well differentiated
^{18}F-FDG	Prognostic value	- Metastatic PPGL - PPGL with *SDHB mutations*	Prognostic value	no	+/–	+++ poorly differentiated

MTC medullary thyroid carcinoma, *PGL* paraganglioma, *PPGL* pheochromocytoma and/or paraganglioma, *CT* calcitonin level, *NET* neuroendocrine tumor, *GEP* gastro-entero-pancreatic

developed and consists a two-dimensional (2D) planar imaging technique using the detection of single-photon-emitting radio-isotopes for establishing the distribution of the radioactive tracer in the human body. The more recent development of three-dimensional (3D) single-photon emission tomography (SPECT), later combined with computerized tomography (SPECT/CT, also known as "hybrid imaging"), has enabled better detection and sensitivity, with more precise localization of lesions thanks to the use of CT.

In parallel, PET/CT has been developed, and proved to have substantial technical advantages over single-photon emission techniques, notably thanks to the use of positron-emitting radio-isotopes specifically used for PET, by exploiting the detection of coinciding pairs of annihilation photons resulting from positron emission. Indeed, after a short distance (approximately 1 mm) in matter, the emitted positron encounters an electron (anti-particle of the positron) resulting in the annihilation of both particles and the emission of two annihilation photons in separate directions at an angle of 180° one from another. This technology enables a substantial improvement in spatial and temporal resolution, resulting in better image quality and shorter acquisition times. For this reason, this modality has seen important development in recent years, and several novel PET tracers have been developed.

PET tracers used in endocrinology

^{18}F-FDG

^{18}F-FDG is currently the most widely used radioactive tracer for routine PET imaging. It consists of fluoro-deoxy-glucose (FDG), a glucose analog, labeled with ^{18}F, a positron-emitting radio-isotope. This compound is accumulated in cells overexpressing glucose membrane transporters (GLUT transporters) and hexokinase, an intracellular glycolytic enzyme [1]. ^{18}F-FDG PET/CT explores cellular glucose metabolism, which is upregulated in certain pathological situations, for instance in certain types of cancer or in inflammatory diseases. The diagnostic and prognostic values of ^{18}F-FDG PET/CT have been demonstrated in several endocrine pathologies, particularly in the fields of thyroid cancer and NETs.

^{18}F-Choline

^{18}F-Choline is a phospholipid membrane precursor (choline) implicated in cellular membrane metabolism, labeled with ^{18}F. This radioactive tracer enables the exploration of conditions involving increased cell proliferation in which cellular membrane production is increased [2]. Initially developed in the field of prostate cancer, its diagnostic value in primary hyperparathyroidism (PHP) has recently been reported.

^{18}F-FDOPA

6-Fluoro-(^{18}F)-L-3,4-dihydroxy-phenylalanine (^{18}F-FDOPA) is an amino-acid labeled with ^{18}F [3]. ^{18}F-FDOPA is transported into cells by the ubiquitous amino-acid transporter LAT-1, before decarboxylation into ^{18}F-dopamine in certain types of cancer, such as paragangliomas (PGLs), pheochromocytomas (PHEOs), and NETs of the midgut. This specific step of intracellular decarboxylation and accumulation in storage vesicles explains the specificity of this tracer for NETs.

^{68}Ga-labeled somatostatin analogs

The ^{68}Ga-labeled somatostatin analog (^{68}Ga-SSA) subgroup contains several tracers sharing a similar structure (^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE), formed by a chelator compound (DOTA) used for labeling with Gallium-68 (^{68}Ga, a positron-emitting radio-isotope), attached to a somatostatin analog oligopeptide (SSA) with specific affinity for somatostatin receptors (sst) [4]. Similarly to scintigraphy with ^{111}In-radiolabeled somatostatin

analogs (SRS), ^{68}Ga-SSA PET/CT explores NETs with sst overexpression (particularly sst2 subtype), with, however, several advantages, such as a higher affinity for the sst2 subtype, a broader affinity profile for different sst subtypes (high affinity for sst2, 3, and 5 for ^{68}Ga-DOTA-NOC), as well as improved spatial resolution thanks to PET/CT technology. Although ^{18}F-labeled tracers are produced by a cyclotron, and are delivered to nuclear medicine departments, radioactive labeling with ^{68}Ga is performed on site, and requires investment in specific infrastructure (automatic synthesis equipment, ^{68}Ga generator), which is relatively costly, and requires operation by qualified personnel. Furthermore, its availability is sparse, as use approval by health authorities is relatively recent.

Gastro-entero-pancreatic (GEP) NETs

GEP NETs are rare tumors, with an annual incidence of approximately 2.5–5 cases per 100,000, which has shown recent increase, probably due to the improvement of imaging techniques [5].

These tumors derive from neuroendocrine cells present all along the digestive tract. They can be divided according to embryological provenance [6]. Tumors originating from the foregut include NETs of the esophagus, duodenum, pancreas, and proximal jejunum. Tumors originating from the midgut include NETs of the distal jejunum, ileum, appendix, and right colon. Tumors of the hindgut include NETs of the transverse and left colon, and of the rectum. GEP NETs can also be divided according to their grade regarding histopathological proliferative index (Ki67) [7]: grade 1 (Ki67 ≤2%), grade 2 (Ki67 between 3 and 20%), and grade 3 (Ki67 >20%), as well as cell differentiation characteristics. Histopathological differentiation and proliferation characteristics have a crucial impact for prognosis assessment and treatment strategy planning. Prognosis greatly varies according to tumor type and proliferative grade, with higher risk of metastatic extension for grade 3 NETs, and the term carcinoma used to describe poorly differentiated tumors according to the latest WHO classification of 2017 [8].

Curative treatment relies on surgery if the tumor is accessible, without metastatic disease, or if metastatic extension is limited and surgically manageable. Other therapeutic approaches include somatostatin analogs (with anti-secretory and/or anti-proliferative intent), targeted therapy (everolimus, sunitinib), chemotherapy (mainly for poorly differentiated and rapidly progressive tumors), and local treatments (such as hepatic arterial embolization). Finally, peptide receptor radionuclide therapy (PRRT) using somatostatin analogs labeled with therapeutic radio-isotopes (^{177}Lu-labeled Dotatate, LUTATHERA®) is emerging as an additional therapeutic option after promising results in the NETTER 1 trial [9].

Optimal detection of primary tumor site and metastatic disease is of major importance for prognosis evaluation and treatment planning. Although conventional imaging and endoscopic ultrasound remain highly accurate, their performances may be sub-optimal for detecting small-sized tumors or tumors located in areas difficult to analyze. Functional imaging is therefore often needed to localize primary and metastatic sites, but also for characterization of tumor type, prognosis assessment, and treatment strategy planning of GEP NETs.

Well-differentiated, low-grade GEP NETs

Staging of these well-differentiated indolent tumors, is typically less accurately assessed by ^{18}F-FDG PET/CT. Scintigraphy with ^{111}In-radiolabeled somatostatin analogs (SRS), a widely available modality, was considered up until recently as the imaging standard for well-differentiated GEP NET staging. However, its diagnostic performance is limited for detecting small-sized lesions or lesions located in areas of high physiological tracer uptake such as the liver and the digestive tract. In recent years, the high diagnostic value of ^{68}Ga-SSA PET/CT has been reported in numerous patient series, with an impact on patient treatment planning [10].

A recent meta-analysis [11] reviewing 10 studies involving 465 patients with GEP or lung NETs found high sensitivity and specificity for tumor staging, 90.9 and 90.6%, respectively. ^{18}F-FDOPA also has good specificity for NETs, however, its diagnostic accuracy varies according to embryological origin of the tumor [12, 13].

Recently, new perspectives have emerged with the development of ^{68}Ga-labeled SST receptor antagonists, which have the advantage of binding to more sst receptor sites than agonists [14]. In a prospective phase II study performed on 12 patients with metastatic low- or intermediate-grade (Grade 1 or 2) GEP NETs, Nicolas et al. reported higher sensitivity for ^{68}Ga-OP202 (an sst receptor antagonist with high affinity for sst2 subtype) compared with ^{68}Ga-DOTATOC, especially for the detection of liver metastases. Image contrast was improved for malignant liver lesions and the lesion-based sensitivity significantly higher with ^{68}Ga-OP202 than with ^{68}Ga-DOTATOC (88% versus 59%, $p < 0.001$) [15].

Foregut NETs

Pancreatic NETs mainly originate from the ductal epithelium cells of the exocrine pancreas. The majority of these tumors are non-functional and diagnosed at an advanced stage, often with initial metastatic disease [16].

^{18}F-FDOPA PET/CT seems of limited value for these tumors. Indeed, Ahlström et al. [17] studied diagnostic performances of ^{11}C-DOPA PET/CT in a series of pancreatic NETs and only 11 out of 22 tumors were detected using this modality. Later on, several studies confirmed these results with the use of ^{18}F-FDOPA [12, 17, 18]. Poor sensitivity of ^{18}F-FDOPA PET/CT for well-differentiated pancreatic NETs is partly due to high physiological tracer uptake in the mature exocrine pancreas. Some studies have reported that the use of carbidopa, a peripheral aromatic L-amino-acid decarboxylase inhibitor reduces physiological pancreatic uptake, thereby increasing ^{18}F-FDOPA PET/CT accuracy for pancreatic NETs [19]. However, there is no consensus regarding the use of carbidopa, and its use is limited by the fact that it is a dispenser's preparation. Furthermore, some studies have reported complete absence of focal pancreatic uptake while using carbidopa, with false-negative results [20]. Other research teams have investigated the potential use of early phase acquisitions. Indeed, additional images acquired 5 min after ^{18}F-FDOPA injection seem to allow better detection of insulinomas, with or without use of carbidopa [21, 22]. Although this modality is poorly sensitive, it remains highly specific, with only one case of false-positive result having been reported in studies, concerning a patient with a pseudopapillary tumor of the pancreas [23].

^{68}Ga-SSA (^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC, ^{68}Ga-DOTATATE) PET/CT seems superior for detecting well-differentiated pancreatic NETs, compared with conventional imaging and SRS®. Kumar et al. [24] have reported in a prospective study including 20 patients with clinically suspected and/or histopathologically proven pancreatic NETs that ^{68}GA-DOTATOC PET/CT was superior for detecting the primary tumor site compared with CT, with a detection rate of 100 versus 75% respectively, as well as for the detection of metastases (detection rate of 100 versus 54% for CT). This result is consistent with another study evaluating ^{68}Ga-DOTATATE PET/CT versus magnetic resonance imaging (MRI), which reported a detection rate of 100 versus 65%, respectively [25]. Despite these good results, the detection of insulinomas remains a pitfall with variable sensitivity of ^{68}Ga-SSA PET/CT ranging from 26 to 85% [26-28], consistent with poor sensitivity of SRS in this setting, probably due to low sst expression in some cases of benign insulinomas [29].

However, the detection of benign insulinomas has recently benefited from the development of glucagon-like peptide-1 receptor (GLP-1R)-targeted imaging. GLP-1R is expressed on benign insulinoma cell surfaces [30] and GLP-1R imaging has been developed using exendin-4 ([Lys40 (Ahx-DOTA-111In) NH2]exendin-4, [Lys40(Ahx-DTPA-111In)NH2]exendin-4, or [Lys40(AhxHYNIC-99mTc/EDDA)NH2]exendin-4), which is a stable agonist of GLP-1R. First results have been reported using SPECT/CT ((111) In-DTPA-exendin-4) in a small series of 19 insulinomas with a high sensitivity (95%) [31]. The same team confirmed these results prospectively with PET/CT imaging using ^{68}Ga-DOTA-exendin-4 PET/CT with an even higher sensitivity than SPECT/CT imaging and a high impact on clinical management [32]. However, despite these excellent results, experience of GLP-1R imaging is actually limited to few centers.

According to these recent data, ^{68}Ga-SSA PET/CT seems to be the best option for detecting pancreatic NETs overall (Fig. 1). This being said, only a few studies have directly compared ^{18}F-FDOPA and ^{68}Ga-SSA radiotracers and only in small patient series. Haug et al. [33] reported better diagnostic performances of ^{68}Ga-DOTATATE PET/CT compared with ^{18}F-FDOPA PET/CT for detecting the primary tumor in pancreatic NETs. On the other hand, Putzer et al. found similar sensitivity values for ^{68}Ga-DOTATOC and ^{18}F-FDOPA PET/CT in a study including four patients [34]. There is, however, no available data comparing ^{18}F-FDOPA PET/CT with use of carbidopa versus ^{68}Ga-SSA PET/CT.

^{68}Ga-DOTANOC PET/CT also seems superior to conventional imaging (CT) for the detection of gastrinomas [35]. These NETs that are usually located within the pancreas or duodenum wall often present with severe secretory syndromes (Zollinger–Ellison syndrome) that may cause complications (digestive hemorrhaging or perforation). The primary tumor is often of small size, with initial lymph node extension or distant metastases at the time of diagnosis. In a small series of patients with a clinical and/or biochemical diagnosis of gastrinoma, ^{68}Ga-DOTANOC PET/CT was more sensitive, specific and more accurate for assessment of lymph node extension than CT [35].

Midgut NETs

Midgut NETs, formerly referred to as "carcinoid tumors", derive from serotonin producing enterochromaffin cells. They typically (but not invariably) present with a clinical and biological carcinoid syndrome [36] and are the most common type of NET.

^{18}F-FDOPA PET/CT has excellent diagnostic performances for midgut NETs, probably because of serotonin production by tumor cells. Indeed, Montravers et al. [12] reported ^{18}F-FDOPA PET/CT having a sensitivity and specificity of 93 and 89%, respectively, for detecting midgut NETs versus 25 and 36%, respectively, for NETs of other embryological origin. It is also superior to other modalities such as CT and MRI or SRS with sensitivity values of 97 versus 65% for CT/MRI and 49% for SRS [37]. This is also true for detecting metastases, ^{18}F-FDOPA PET/CT having excellent sensitivity compared with CT or SRS in this setting [38].

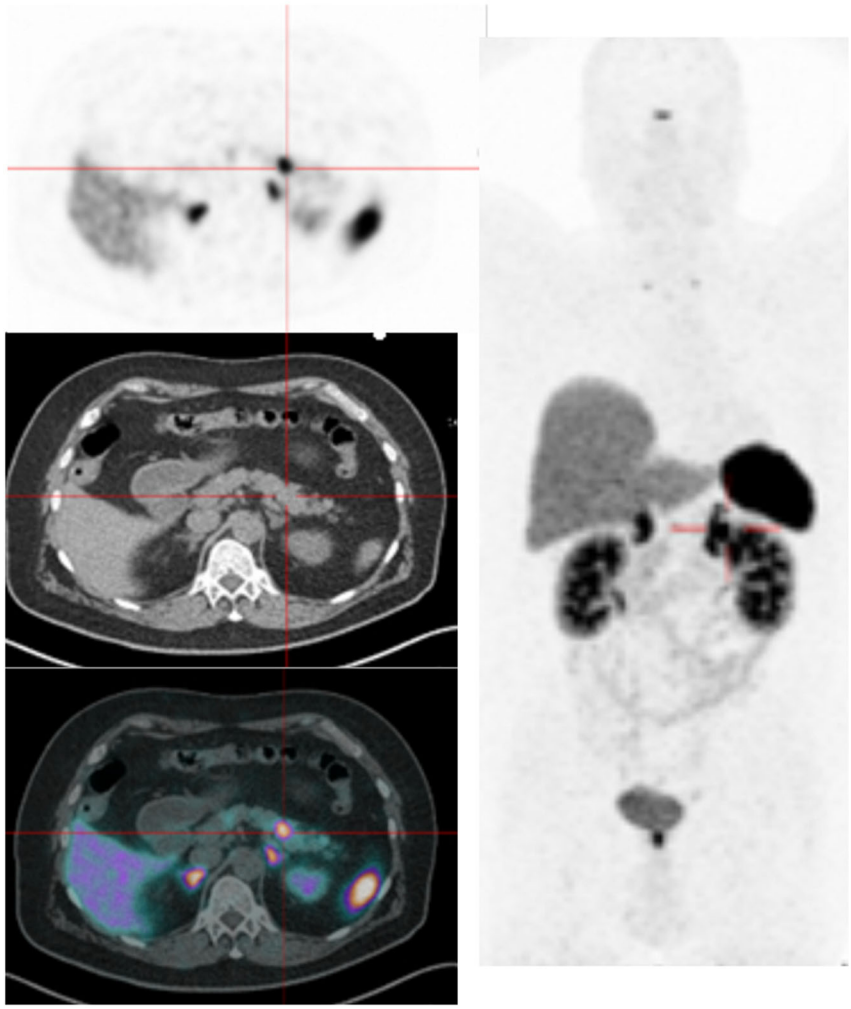

Fig. 1 ^{68}Ga-DOTATOC PET/CT imaging detecting a 12-mm well-differentiated NET located in the body of the pancreas (SUVmax = 100)

^{68}Ga-SSA PET/CT also seems promising. Ilhan et al. [39] reported sensitivity and specificity of 68 and 100%, respectively, for ^{68}Ga-DOTATE PET/CT in 26 patients with NETs of the ileum needing complementary surgery subsequently to incomplete removal after initial surgery. Of the seven false-negative results, five were due to tumors with a size smaller than 1 cm. These authors also reported sensitivity of 88% for the detection of invaded lymph nodes, as well as high accuracy for detecting metastases of the liver, lung and/or bone. To date, there is only little data comparing ^{18}F-FDOPA and ^{68}GA-SSA PET/CT in midgut NETs [33, 40] with a tendency for ^{18}F-FDOPA PET/CT being superior. ^{18}F-FDOPA PET/CT is therefore considered as the first-line imaging modality for the staging of well-differentiated NETs of the ileum with serotonin secretion. However, ^{18}F-FDOPA PET/CT does not have any proven prognostic value and does not allow for the "theranostic" approach that is possible with ^{68}Ga-SSA imaging.

Hindgut NETs

Hindgut NETs are usually more aggressive than those of the midgut [7] and are often diagnosed subsequently to colonoscopies, upon histopathological examination of resected polyps. To the best of our knowledge, apart from a few cases reported in large series of patients with GEP NETs of all provenance [33], there has been no study investigating the use of ^{18}F-FDOPA PET/CT in hindgut NETs. According to tumor grade, ^{18}F-FDG PET/CT [41] and/or ^{68}Ga-SSA PET/CT [42] appear to be useful for tumor staging.

Aggressive, poorly differentiated GEP NETs

^{18}F-FDG PET/CT should be the first-line imaging modality for grade 3 GEP NETs [37, 43, 44]. This modality is the most sensitive for the staging of these tumors, which have lost neuroendocrine differentiation characteristics such as

sst overexpression by tumor cells. Indeed, high ^{18}F-FDG uptake seems to indicate poor cell differentiation and high tumor aggressiveness.

^{18}F-FDG PET/CT also seems superior for "high grade 2" GEP NETs, with sensitivity of 77 versus 43% for SRS [45].

In some cases, ^{18}F-FDG uptake may also vary according to tumor location, with more frequent uptake in pancreatic tumors, particularly in the absence of secretory syndromes, which is often associated with less differentiated tumors and worse prognosis [46, 47].

However, it should be noted that this modality may also be of interest for well-differentiated tumors. Indeed, ^{18}F-FDG uptake by tumor cells, even for well-differentiated or low-grade tumors, in particular in pancreatic tumors, seems to be related to worse prognosis [48]. ^{18}F-FDG PET/CT may also be used to detect cellular heterogeneity of tumor burden within the same patient, or the transformation of a low grade tumor into an aggressive tumor [49].

Lung NETs

Lung NETs are the second most frequent type of NET (20% of cases) after GEP NETs, and account for 1–3% of lung cancers [50]. They derive from the neuroendocrine cells of the respiratory tract epithelium [51] and are endobronchial in 90% of cases [52]. They are divided into four subgroups: typical carcinoid and atypical carcinoid tumors (which are well differentiated), large cell neuroendocrine carcinomas, and small cell lung carcinomas, which are poorly differentiated and rapidly progressive tumors, with frequent metastatic spread and poor prognosis [51].

They may occur sporadically or as part of hereditary syndromes such as type 1 multiple endocrine neoplasia (MEN-1) syndrome [50].

Curative therapy mainly relies on surgical treatment when feasible [50, 51]. In other cases, therapeutic options include chemotherapy, with or without radiation therapy, or targeted therapies such as (mammalian Target Of Rapamycin) mTOR inhibitors. Somatostatin analogs may also be used, as well as PRRT [50] because these tumors overexpress sst receptors in over 80% of cases, with sst expression increasing with the level of differentiation of the tumor [51, 52].

Tumor localization and detection of metastatic disease is therefore essential for treatment planning. Conventional imaging such as CT or MRI is widely used but is not specific for the diagnosis of lung NETs. For well-differentiated tumors, functional imaging using radiolabeled SSA (i.e., SRS or ^{68}GA-SSA PET/CT) is very helpful. For high-grade poorly differentiated tumors, ^{18}F-FDG PET/CT remains the standard for functional imaging. As for ^{18}F-FDOPA PET/CT, this technique has not been thoroughly investigated, with a few studies mainly focusing on well-differentiated lung NETs showing disappointing results [37], and is therefore not recommended for the staging of these tumors [53].

Well-differentiated lung NETs

This group includes typical carcinoid and atypical carcinoid tumors. These tumors show highly increased sst receptor expression. SRS, which was initially used, has good sensitivity ranging up to 93% for the detection of primary tumor site, surpassing conventional imaging [54].

^{68}GA-SSA PET/CT has shown promising results in this setting. Ambrosini et al. [55] evaluated ^{68}GA-DOTANOC PET/CT in a series of 11 patients, and were able to detect lesions in 9 patients. Also, this technique was more informative than CT in 9 out of 11 patients (higher lesion detection rate, or conversely exclusion of lesions appearing ambiguous for metastasis on CT), and modified treatment strategy for 3 patients. Overall, ^{68}GA-SSA PET/CT appears to be the best modality for this type of tumor. Indeed, thanks to better special resolution, its sensitivity is higher than SRS for small size lesions [56, 57]. It has also better diagnostic performances than ^{18}F-FDG PET/CT for well-differentiated typical carcinoid tumors [58–60].

Poorly differentiated lung NETs

As previously stated, this group is comprised of large cell neuroendocrine carcinomas and small cell lung carcinomas. These high-grade tumors have lower sst expression. ^{18}F-FDG PET/CT has therefore a better sensitivity for this tumor type than ^{68}Ga-SSA PET/CT [58], with sensitivity ranging up to 100% for small cell lung carcinomas [61].

^{18}F-FDG PET/CT also has prognostic value in small cell lung carcinomas. Substantially lower survival rates have been reported in ^{18}F-FDG PET/CT-positive patients as compared with ^{18}F-FDG PET/CT-negative patients [61], with measured SUVmax values inversely correlated with patient survival rates [61].

Unknown primary tumor

Most NETs presenting with initial metastatic spread concern pancreatic and midgut NETs [62]. Identification of the primary tumor site is essential for treatment planning, notably for primary tumor resection, which may improve patient survival and quality of life [13, 63], as well as for determining the appropriate systemic treatment, pancreatic NETs having usually better response to chemotherapy than midgut NETs [64]. However, detecting the primary tumor

site may be challenging, particularly because of the frequently small tumor size.

Some authors have suggested that ^{18}F-FDOPA PET/CT may be an effective imaging tool for the detection of the primary tumor, particularly when conventional imaging and SRS remain inconclusive [13]. Also, ^{18}F-FDOPA PET/CT positivity seems to be correlated with elevated plasmatic chromogranin and serotonin levels, which may imply the presence of a serotonin producing midgut NET as the primary tumor.

Other studies have evaluated ^{68}GA-SSA PET/CT in this setting. In three studies, ^{68}GA-SSA PET/CT was able to identify the primary tumor site in around 60% of patients with initially metastatic histopathologically proven NETs with no primary tumor identified using conventional imaging (with similar findings concerning sensitivity for midgut or pancreatic primary tumors) [65–67].

Medullary thyroid carcinoma

Medullary thyroid carcinoma (MTC) is a well-differentiated thyroid cancer of non-follicular origin, and represents a fairly rare form of thyroid cancer (1–5%) [68]. It derives from C cells in the thyroid gland, responsible for calcitonin production. Therefore, the plasmatic calcitonin level constitutes a reliable marker for the follow-up of tumor evolution, as well as the plasmatic carcino-embrionic antigen (plasmatic CEA). MTC frequently presents with lymph node invasion or metastatic disease [69], which may be challenging to detect as it may present in the form of fine miliary type hepatic or bone invasion. Hereditary forms occur in 25% of all cases, as part of multiple endocrine neoplasm syndromes type 2A and 2B (MEN-2A and MEN-2B), or as part of familial medullary thyroid cancer syndrome (FMTC syndrome). It is frequently associated with a mutation of the *RET* gene, either as a germ-line mutation in hereditary syndromes, or as a somatic mutation in 50% of sporadic forms [68].

The therapeutic impact of PET/CT as a first-line imaging tool for initial tumor staging has yet to be established [3], and nowadays neck ultrasound is used as the standard imaging modality. However, in cases of residual disease after surgery or disease recurrence, generally established by elevation or absence of decrease of plasma calcitonin levels, PET/CT plays an important role in evaluating residual tumor burden and establishing whether this burden is surgically manageable. In these patients, PET/CT is also useful for follow-up and for evaluating therapeutic response in the case of systemic treatments.

^{18}F-FDOPA PET/CT for MTC

More than a decade ago, a prospective study showed the superiority of several conventional imaging procedures for the detection of MTC recurrence as compared with bone scintigraphy and ^{18}F-FDG PET/CT. The most sensitive imaging procedures were neck ultrasonography (US) for neck exploration, CT for assessment of lung and mediastinal lymph node metastases and contrast enhanced MRI for assessing liver extension [70]. Bone scintigraphy had the highest sensitivity for bone metastasis detection (65%) but there was no direct comparison with ^{18}F-FDOPA PET/CT.

Since then, several studies have evaluated ^{18}F-FDOPA PET/CT (Table 2), which is seemingly the most sensitive and specific imaging modality for detecting residual disease in patients with high plasmatic calcitonin levels [71–83] (Fig. 2), as reported in a recent meta-analysis including 139 patients showing a 66% detection rate on a per patient basis and 71% on a per lesion basis [84]. ^{18}F-FDOPA PET/CT performed at least as well as conventional imaging in different studies with the advantage of a 3D whole body exploration in a single procedure [75].

^{18}F-FDOPA PET/CT is also superior to ^{18}F-FDG or ^{68}Ga-SSA PET/CT for re-staging in patients with known residual or recurrent disease [71, 84, 85]. Importantly, this imaging modality is most effective for calcitonin levels above 150 pg/ml. Indeed, in a prospective study including 17 patients comparing ^{18}F-FDG and ^{18}F-FDOPA PET/CT, Romero-Lluch et al. reported sensitivity for ^{18}F-FDOPA PET/CT of 91% for patients with calcitonin levels above 150 pg/ml, against sensitivity of 29% for calcitonin levels below this value [72].

Also, it should be noted that to obtain optimal accuracy in MTC, ^{18}F-FDOPA PET/CT requires an additional early phase acquisition (15 min after tracer injection) because of rapid tracer washout in certain MTC lesions [85, 86].

Revised guidelines from the American Thyroid Association published in 2015 [87] do not recommend performing PET imaging for recurrent and metastatic MTC and prefer an imaging work-up including several conventional imaging modalities such as neck US, thoracic CT, as well as MRI for liver and bone assessment, in contradiction with the previous version published in 2009 [88]. Nevertheless, the European Society of Nuclear Medicine (EANM) refused to endorse these guidelines owing to literature evidence [68]. Overall, ^{18}F-FDOPA PET/CT appears to be of interest at least for post-operative staging when disease recurrence is suspected upon biomarker elevation (calcitonin > 150 pg/ml) and could guide the choice and interpretation of conventional imaging (Fig. 3).

Table 2 Main studies reporting 18F-FDOPA PET detection rate of relapsing MTC related to the serum calcitonin value

Study	*N*	Modality	Detection rate or sensitivity				
			Per patient	Per lesion	CT < 150	CT ≥ 150	CT ≥ 1000
Romero-Lluch[a] [72]	19	PET/CT	67%	NP	29%	91%	NP
Caobelli [74]	60	PET/CT	73%	NP	NP	NP	NP
Archier [75]	86	PET/CT	76%	NP	NP	61%	79%
Sesti [76]	39	PET	52%	NP	NP	79%	NP
Treglia [71]	18	PET/CT	72%	85%	100%	69%	100%
Verbeek [73]	47	PET	38%	75%	NP	NP	NP
Kauhanen[a] [77]	19	PET/CT	58%	52%	0%	79%	83%
Luster [78]	25	PET/CT	74%	NP	37%	100%	100%
Marzola [79]	18	PET/CT	83%	76%	–	–	–
Beheshti[a] [80]	26	PET/CT	74%	94%	50%	76%	83%
Koopmans[a] [81]	21	PET	62%	71%	20%	75%	92%
Beuthien [82]	15	PET	47%	–	33%	56%	0%
Hoegerle[a] [83]	11	PET	50%	63%	NP	50%	80%

CT calcitonine level (pg/ml), *NP* not performed

[a]Prospective studies

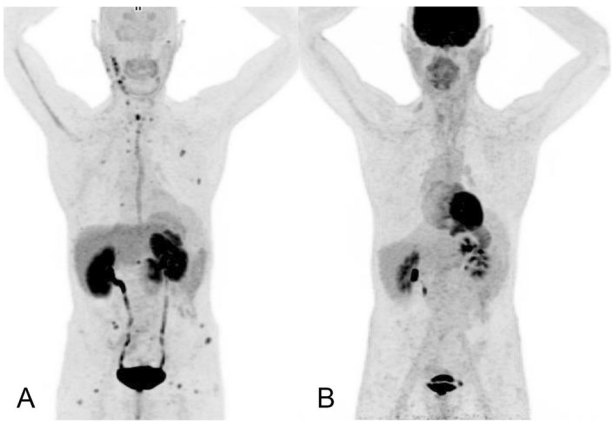

Fig. 2 Post-operative medullary thyroid carcinoma remnant (plasma calcitonin levels, 1800 ng/ml) in a 67-year old man. Multiples metastases are detected on ^{18}F-FDOPA PET/CT (**a**) contrasting with a completely negative ^{18}FDG PET/CT imaging (**b**)

^{18}F-FDG PET/CT for MTC

Although ^{18}F-FDOPA PET/CT appears to be more sensitive than ^{18}F-FDG PET/CT for the detection of residual disease, several studies have reported the prognostic value of ^{18}F-FDG PET/CT in MTC, showing a correlation between tracer uptake intensity and the shortening of plasmatic calcitonin doubling time [89], a known progression/prognostic indicator in MTC [73, 90]. However, as underlined by Treglia et al. [56] in their meta-analysis, there is an important variability of ^{18}F-FDG PET/CT detection rates in MTC according to calcitonin and CEA levels but also doubling times. Indeed, the patient-based detection rate for ^{18}F-FDG PET/CT derived from 24 studies comprising 538 patients with suspected MTC recurrence was of 59% overall, while it increased to 69% when CEA was superior to 5 ng/ml, to 75% for patients with serum calcitonin levels above 1000 ng/l, to 76% for patients with a calcitonin doubling time of <12 months and even up to 91% when the CEA doubling time was <24 months [56].

^{18}F-FDG PET/CT may therefore be of complementary use to ^{18}F-FDOPA PET/CT in the staging and prognostic assessment of aggressive forms of MTC.

PHEOs and PGLs

PHEOs and PGLs (PPGLs) constitute a group of NETs originating from neuroendocrine cells of the nervous system deriving from the neural crests. PPGLs deriving from the sympathetic nervous system (sympathetic PPGLs) originate either from chromaffine progenitor cells of the adrenal medulla in 80% of all cases [and are then called PHEOs] or sympathetic paravertebral ganglia of the thorax, abdomen or pelvis in 20% of all cases. Sympathetic PPGLs often account for increased production of catecholamines, which induce some of the clinical symptoms related to these types of tumors (hypertension, headache, sweating, pallor…) and allow biological detection, for instance by measurement of urinary metanephrine levels. Conversely, parasympathetic PGLs are predominantly non-secretory (4% of tumors are secretory), which explains why these tumors are often non-symptomatic. Their most frequent site of occurrence is the head and neck region. Although most PPGLs are benign, 10% of PHEOs and 25–40% of PGLs are malignant [91, 92], and there are no established histopathological criteria for defining malignancy, which remains defined by the

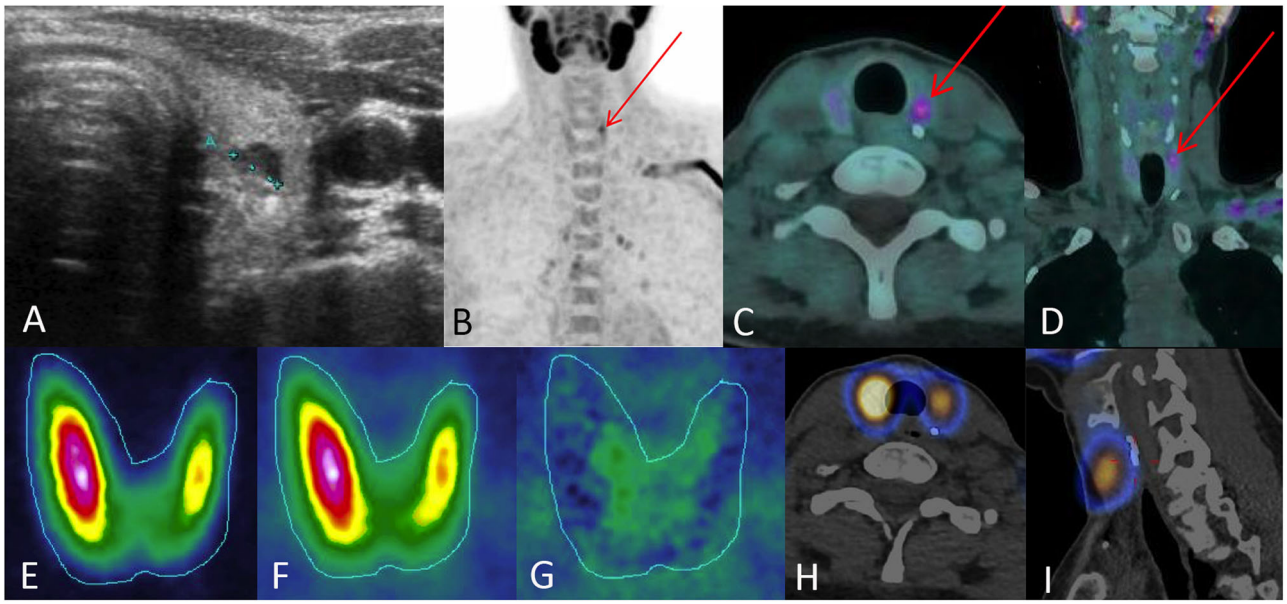

Fig. 3 Persistent primary hyperparathyroidism after a first upper left parathyroid adenoma resection in a 57-year old woman. Imaging work-up showing persistence of an intrathyroid remnant of the abnormal left P3 parathyroid gland visualized on ultrasonography (US) (**a**) and confirmed on ^{18}F-F-Choline PET (maximal intensity projection (**b**), axial fusion (**c**), coronal fusion (**d**) but not on ^{99m}Tc-SestaMIBI simple phase/dual tracer scintigraphy (planar sodium pertechnetate thyroid scintigraphy (**e**), planar ^{99m}Tc-MIBI scintigraphy (**f**), substraction images (**g**)) nor on ^{99m}Tc-MIBI-SPECT/CT showing a high thyroid uptake (axial fusion (**h**) and sagittal fusion (**i**))

occurrence of a metastatic lesion according to the 2004 WHO pathological criteria [93]. About 40% of PPGLs are due to germ-line mutations [94] and 16 genes with predisposing mutations have been identified (*RET, NF1, VHL, SDHA, SDHB, SDHC, SDHD, SDHAF2, MAX, TMEM127, FH, MDH2, SLC25A11, GOT2*, *HIF2*…) [95].

Genetic forms predispose to multiple and sometimes malignant forms of PPGLs. Surgery is the only curative treatment but may be challenging for certain tumor locations and may present a risk of nerve or vascular damage, which increases with tumor size. Therefore, these patients require thorough imaging exploration with several goals: precise localization of the PPGL lesion, identification of other tumor sites in the case of multiple lesion predisposition syndromes, initial staging regarding possible metastatic lesions, assessment of therapeutic response for malignant PPGLs undergoing systemic therapy and screening for patients with a genetic predisposition and no PPGL having yet been identified (family members).

CT and MRI constitute highly sensitive modalities for PPGL detection. However, they may not always establish the diagnosis of PPGL, due to lower specificity as compared with metabolic imaging [95]. Nuclear medicine techniques have enabled the exploration of these tumors for many years, with the benefit of the highly specific metabolic information it provides and of whole body exploration [96].

PHEOs

^{18}F-FDOPA PET/CT is the most sensitive imaging modality for these tumors, and even though its superiority to ^{123}I-MIBG has yet to be clearly demonstrated [3], it is less prone to pharmacological interactions with patient treatments. ^{18}F-FDOPA PET/CT has numerous advantages such as a shorter acquisition time and lower physiological uptake in the adrenal glands, which may confer an advantage over ^{68}Ga-SSA PET/CT, notably for detecting multiple lesions in patients with hereditary syndromes involving germ-line mutations of *RET*, *VHL*, or *NF1* [95].

PGLs

^{18}F-FDOPA PET/CT is a highly effective imaging tool for detecting cervical PGLs, with reported sensitivity and specificity values > 95% [3]. For this reason, this modality is considered as the standard imaging technique for cervical lesions, especially for *SDHD* mutation carriers [97–99].

For abdominal sympathetic PGLs or metastatic PGLs, ^{18}F-FDOPA PET/CT has lower diagnostic performances, with several false-negative cases reported for abdominal retroperitoneal PGLs, and poor sensitivity for detecting metastatic lesions. Indeed, in a large prospective study by Timmers et al. [100], ^{18}F-FDG PET/CT was superior for detecting metastatic lesions, particularly in *SDHB* mutation carriers.

More recently, ^{68}Ga-SSA PET/CT has shown promising results and was reported superior to ^{18}F-FDOPA PET/CT in various situations including cervical lesions [101, 102], or all extra-adrenal locations combined [103]. ^{68}Ga-SSA PET/CT also appears to be highly accurate for metastatic PPGLs, particularly in *SDHB* mutation carriers [104]. However, these studies only included small numbers of patients and are mostly retrospective. The exact place for ^{68}Ga-SSA PET/CT remains in discussion.

Imaging strategy according to genetic status

Hereditary forms of PPGLs may present as a variety of tumor locations and secretory profiles, and some authors have therefore recommended specific metabolic imaging modalities according to genetic status when already known [95, 96]. However, this is rarely the case prior to surgery for patients being treated for a first tumor. Conversely, in the case of tumors in patients with known predisposing mutations (family members or second tumors), it has been recently proposed to favor ^{18}F-FDOPA PET/CT for patients with known mutations of *RET*, *NF1*, *TMEM127*, *MAX*, *VHL*, and *HIF2A* while favoring ^{68}Ga-SSA PET/CT (if available) or ^{18}F-FDG PET/CT (in the absence of ^{68}Ga-SSA availability) for *SDHx, FH*, and *SLC25A11* mutation carriers.

A consensual imaging strategy for screening tumors in known predisposed asymptomatic *SDHx* mutation carriers (family members) identified after genetic screening has yet to be established. MRI has the significant advantage of using a magnetic field to generate images, without radiation exposure, which is an important argument for the use of this modality in the setting of a life-long follow-up required in these patients. Some authors have suggested that MRI could be performed every 3 years as an effective screening strategy [95]. One retrospective study including 30 patients found good sensitivity for ^{18}F-FDG PET/CT combined with cervical magnetic resonance angiography (MRA) [105]. ^{18}F-FDOPA and ^{68}Ga-SSA PET/CT have yet to be investigated in this setting but would probably be of great interest.

PHP

PHP is one of the most frequent endocrine conditions, with a prevalence in the general population of 0.86%, a rapidly increasing incidence, and a predominance in women (sex ratio 3–4 F:1 M) [106].

The increased production of parathyroid hormone (PTH) by the parathyroid glands is secondary to an individual adenoma (single-gland disorder or SGD) in 80% of cases, or in the case of multiglandular disorder (MGD) by multiple adenomas or multiglandular hyperplasia accounting for 20% of cases [106]. Parathyroid carcinomas are exceptional (<1%).

Surgical treatment should only be undergone in patients with clinical symptoms or in patients who may develop PHP complications as defined by the 2014 international recommendations (according to degree of hypercalcemia, age, bone density loss, history of vertebral bone fracture, or kidney failure with (glomerular filtration rate) GFR < 60 ml/min) [107]. Surgery is the only curative treatment for PHP with high success rates (95%) and low complication rates (<1 to 3%) [108]. The traditional surgical technique consists in bilateral neck exploration (BNE), which assesses all four parathyroid glands during the procedure. However, more recently, minimally invasive parathyroidectomy (MIP) techniques have become a new standard, enabling a targeted surgical approach on one gland in the case of SGD. MIP has several advantages over BNE, such as the possibility of outpatient surgery, a shorter procedure duration and lower post-operative complication rates [109]. MIP should only be considered if preoperative imagery (neck ultrasound and ^{99m}Tc-SestaMIBI scintigraphy) is conclusive for the presence of SGD and in agreement for its localization. In other cases, BNE remained up until recently the standard procedure [107].

The diagnosis of PHP is established upon the measurement of plasma levels of calcium, PTH, 25-OH-vitamin D, and urinary calcium. Imaging should only be performed after biological diagnosis of PHP and only in patients requiring surgical treatment, with the intent of guiding the surgical procedure and to assess feasibility of MIP in the case of SGD.

The usual first-line imaging consists in neck ultrasound and ^{99m}Tc-SestaMIBI parathyroid scintigraphy, with sensitivity values ranging from 66 to 90% depending on ^{99m}Tc-SestaMIBI scintigraphy protocols (double-isotope subtraction, double phase, with or without SPECT and CT) and presence of SGD versus MGD [110–113]. When both modalities are in agreement for SGD and its location, MIP can be performed. In the case of MGD or discrepancy between the two preoperative imaging techniques, BNE was up until recently the standard approach.

PET/CT using Choline tracers (^{11}C-Choline and ^{18}F-Choline) is an important tool used for early detection of prostate cancer recurrence, and subsequently to its development in this field several cases of intense cervical tracer uptake within parathyroid adenomas have been reported [114–116]. ^{11}C-Choline and ^{18}F-Choline are both interesting for the detection of abnormal parathyroid glands [117] but in view of its wider availability (due to slower radioactive decay of ^{18}F), there have been more studies on ^{18}F-Choline in recent years (Table 3) [118–133].

Table 3 ^{18}F-F-Choline PET tracer studies for primary hyperparathyroidism involving at least 10 patients

Study	*N* patients	Design	Population		Modality	Acquisition time (min)	Lesion-based sensitivity (%)
			Previous surgery	Neg/disc imaging			
Lezaic [118]	24	Prospective	No	No	PET/CT	5 and 60	–
Michaud [124]	12	Retrospective	No	Yes	PET/CT	Immediately	92
Michaud [125]	17	Retrospective	No	Yes	PET/CT	Immediately	96
Rep [127]	43	Retrospective	No	No	PET/CT	5, 60, and 120	98
Kluijfhout [128]	44	Retrospective	No	Yes	PET/CT	30	94
Hocevar [119]	151	Retrospective	No	No	PET/CT	5 and 60	98
Kluijfhout [129]	10	Prospective	No	Yes	PET/MR	Dynamic 40 min	90
Quak [130]	25	Prospective	Yes	Yes	PET/CT	60	90
Grimaldi [126]	27	Prospective	Yes	Yes	PET/CT	30	76
Beheshti [131]	100	Prospective	No	No	PET/CT	60	94
Fischli [132]	39	Retrospective	Yes	Yes	PET/CT	45	88
Huber [133]	26	Retrospective	No	Yes	PET/CT or PET/MR	NP	96
Amadou [134]	29	Retrospective	Yes	Yes	PET/CT	60	96

Neg/disc imaging negative or discordant imaging, *N* number, NP not provided

^{18}F-Choline PET/CT versus first-line imaging

In 2014, Lenzaic et al. prospectively compared the diagnostic performances of ^{18}F-Choline PET/CT and parathyroid scintigraphy in a pilot study including 24 PHP patients [118]. They reported sensitivity on a per lesion basis of 94% for adenomas and 91% for parathyroid hyperplasia for ^{18}F-Choline PET/CT versus 82 and 50%, respectively, for ^{99m}Tc-SestaMIBI scintigraphy.

In a retrospective study including 151 patients [119], ^{18}F-Choline PET/CT had excellent performances for guiding MIP without intraoperative PTH measurements, with a surgical success rate of 95%. ^{18}F-Choline PET/CT identified SGD accessible to MIP in 83% of patients with PPV above 95% whereas single tracer ^{99m}Tc-SestaMIBI scintigraphy (using SPECT/CT) and neck ultrasound only identified SGD in 62 and 61% of patients, respectively.

Furthermore, a recent prospective study including 36 patients reported lower radiation exposure for ^{18}F-Choline PET/CT (2.8 mSv) compared with scintigraphy protocols, with the highest radiation exposure for double-isotope subtraction techniques (which require a second tracer injection for thyroid mapping in addition to the ^{99m}Tc-SestaMIBI injection) attaining 7.4 mSv (versus 6.8 mSv for double phase ^{99m}Tc-SestaMIBI scintigraphy with SPECT/CT). The low-dose CT performed in hybrid techniques only accounted for a small proportion of total radiation exposure (1.4 mSv for SPECT/CT and 0.8 mSv for PET/CT) [121]. However, these radiation exposure levels remain relatively low compared with 4D parathyroid CT that usually reaches 10 mSv.

Discrepancy in first-line imaging

One of the challenges in preoperative detection of parathyroid adenomas consists in the situation of discrepancy between PHP imaging techniques, which prevent the possibility of MIP, and increase the possibility of BNE failure [122, 123]. Recent data have reported ^{18}F-Choline PET/CT as an effective imaging tool in this setting.

A French team published two prospective studies involving the same patient population [124, 125] while focusing on the value of ^{18}F-Choline PET/CT in patients with discrepancy in first-line imaging techniques (neck ultrasound and ^{99m}Tc-SestaMIBI planar imaging without SPECT/CT) and reported in their most recent study sensitivity on a per lesion basis of 94% in 17 patients including 11 PHP patients and 6 secondary hyperparathyroidism patients [125]. This study reported substantially higher diagnostic performances for ^{18}F-Choline PET/CT compared with neck ultrasound on per lesion and per patient basis. There was a trend for superiority of ^{18}F-Choline PET/CT over ^{99m}Tc-SestaMIBI scinitigraphy but the difference was not always significant (sensitivity of 83% for ^{99m}Tc-SestaMIBI scintigraphy versus 96% for ^{18}F-Choline PET/CT, $p > 0.2$).

Recurrent disease (Fig 3)

In a retrospective study including 27 patients, 9 (26%) underwent ^{18}F-Choline PET/CT for persistent or recurrent disease, of which only 3 underwent a second surgery [6 did not undergo surgery for refusal ($n = 1$), comorbidity ($n = 2$), or stabilization of plasmatic calcium ($n = 3$)], with

correct evaluation by ^{18}F-Choline PET/CT in all 3 patients and sensitivity of 100% [126].

Very recently, a single-center retrospective study focused exclusively on recurrent or persistent disease [134]. In the 29 patients included in the study, ^{18}F-Choline PET/CT allowed the identification and removal of an abnormal gland in 21 patients, 12 of whom had negative or discordant first-line imaging, resulting in a 73% cure rate.

^{18}F-Choline PET/MRI

^{18}F-Choline PET/MRI is a promising novel modality for parathyroid imaging, combining simultaneously acquired parathyroid MRI as the localizing modality (high contrast resolution and absence of radiation exposure) and ^{18}F-Choline PET bringing important functional information. Only few studies have been conducted but first results are promising, with high sensitivity and PPV values respectively of 95 and 100% in the setting of first-line imaging [133] (study combining PET/CT and PET/MRI data) and 90 and 100% in the setting of second line imaging after discrepancy of first-line imaging (neck ultrasound and ^{99m}Tc-SestaMIBI scintigraphy) [129].

Conclusion

For several decades, functional imaging has played an important role in endocrinology. The more recent development of PET/CT technology and emergence of novel tracers have resulted in considerable improvement in the sensitivity of these imaging techniques, making them essential in the evaluation of NETs, for tumor localization, as well as staging, prognosis assessment and treatment response evaluation, with an important impact on therapeutic decision making and patient outcome.

However, these novel PET tracers (^{18}F-FDOPA, ^{68}GA-SSA, ^{18}F-Choline) have limited availability and ^{68}GA-SSA and ^{18}F-Choline even though very promising, still require evaluation in larger patient studies.

Along with the emergence of ^{68}Ga-labeled tracers, the so-called “theranostic” approach is developing, using the same peptide used for functional imaging but labeled with a therapeutic radio-isotope (α or β-emitting isotope) for PRRT, which enables systemic targeted treatment of neoplastic lesions showing high tracer uptake on functional imaging.

There are still numerous unmet medical needs, such as the need for specific and widely available tracers for the exploration of pituitary adenomas [135]. Better availability of all these novel tracers is to be expected in upcoming years, as well as the development of PRRT. The discussion remains open concerning the exact position of these new techniques among existing strategies for treatment planning, follow-up, and treatment response evaluation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All patients signed an inform consent stipulating that their images could be used in a research context after anonymized.

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. R. Boellaard, R. Delgado-Bolton, W.J.G. Oyen et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur. J. Nucl. Med Mol. Imaging **42**, 328–354 (2015). https://doi.org/10.1007/s00259-014-2961-x
2. V. Cuccurullo, G.D. Di Stasio, L. Evangelista, G. Castoria, L. Mansi, Biochemical and pathophysiological premises to positron emission tomography with Choline radiotracers. J. Cell. Physiol. **232**, 270–275 (2017). https://doi.org/10.1002/jcp.25478
3. C. Lussey-Lepoutre, E. Hindié, F. Montravers et al. The current role of 18F-FDOPA PET for neuroendocrine tumor imaging. Médecine Nucl. **40**, 20–30 (2016). https://doi.org/10.1016/j.mednuc.2016.01.003
4. J.J.M. Teunissen, D.J. Kwekkeboom, R. Valkema, E.P. Krenning, Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours. Endocr. Relat. Cancer **18**(Suppl 1), S27–S51 (2011). https://doi.org/10.1530/ERC-10-0282
5. I.M. Modlin, K. Oberg, D.C. Chung et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. **9**, 61–72 (2008). https://doi.org/10.1016/S1470-2045(07)70410-2
6. J.-Y. Scoazec, A. Couvelard, Ppour le réseau TENpath (réseau national d’expertise pour le diagnostic anatomopathologique des tumeurs neuroendocrines malignes de l’adulte, sporadiques et familiales). [The new WHO classification of digestive neuroendocrine tumors]. Ann. Pathol. **31**, 88–92 (2011). https://doi.org/10.1016/j.annpat.2011.01.001
7. A. Dolcetta-Capuzzo, V. Villa, L. Albarello et al. Gastroenteric neuroendocrine neoplasms classification: comparison of prognostic models. Cancer **119**, 36–44 (2013). https://doi.org/10.1002/cncr.27716
8. G. Klöppel, Neuroendocrine neoplasms: dichotomy, origin and classifications. Visc. Med. **33**, 324–330 (2017). https://doi.org/10.1159/000481390
9. J. Strosberg, G. El-Haddad, E. Wolin et al. Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N. Engl. J. Med. **376**, 125–135 (2017). https://doi.org/10.1056/NEJMoa1607427
10. M.M. Graham, X. Gu, T. Ginader, P. Breheny, J.J. Sunderland, 68Ga-DOTATOC imaging of neuroendocrine tumors: a systematic review and metaanalysis. J. Nucl. Med. **58**, 1452–1458 (2017). https://doi.org/10.2967/jnumed.117.191197
11. S.A. Deppen, J. Blume, A.J. Bobbey et al. 68Ga-DOTATATE compared with 111In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. J. Nucl. Med. **57**, 872–878 (2016). https://doi.org/10.2967/jnumed.115.165803
12. F. Montravers, D. Grahek, K. Kerrou et al. Can fluorodihydroxyphenylalanine PET replace somatostatin receptor

scintigraphy in patients with digestive endocrine tumors? J. Nucl. Med. **47**, 1455–1462 (2006)
13. A. Imperiale, E. Rust, S. Gabriel et al. 18F-fluorodihydroxyphenylalanine PET/CT in patients with neuroendocrine tumors of unknown origin: relation to tumor origin and differentiation. J. Nucl. Med. **55**, 367–372 (2014). https://doi.org/10.2967/jnumed.113.126896
14. M. Fani, G.P. Nicolas, D. Wild, Somatostatin receptor antagonists for imaging and therapy. J. Nucl. Med. **58**(Suppl 2), 61S–66S (2017). https://doi.org/10.2967/jnumed.116.186783
15. G.P. Nicolas, N. Schreiter, F. Kaul et al. Sensitivity comparison of 68Ga-OPS202 and 68Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine tumors: a prospective phase II imaging study. J. Nucl. Med. **59**, 915–921 (2018). https://doi.org/10.2967/jnumed.117.199760
16. T.R. Halfdanarson, K.G. Rabe, J. Rubin, G.M. Petersen, Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann. Oncol. J. Eur. Soc. Med Oncol. **19**, 1727–1733 (2008). https://doi.org/10.1093/annonc/mdn351
17. H. Ahlström, B. Eriksson, M. Bergström, P. Bjurling, B. Långström, K. Oberg, Pancreatic neuroendocrine tumors: diagnosis with PET. Radiology **195**, 333–337 (1995). https://doi.org/10.1148/radiology.195.2.7724749
18. F. Montravers, K. Kerrou, V. Nataf et al. Impact of fluorodihydroxyphenylalanine-18F positron emission tomography on management of adult patients with documented or occult digestive endocrine tumors. J. Clin. Endocrinol. Metab. **94**, 1295–1301 (2009). https://doi.org/10.1210/jc.2008-1349
19. O.C. Neels, K.P. Koopmans, P.L. Jager et al. Manipulation of [11C]-5-hydroxytryptophan and 6-[18F]fluoro-3,4-dihydroxy-L-phenylalanine accumulation in neuroendocrine tumor cells. Cancer Res. **68**, 7183–7190 (2008). https://doi.org/10.1158/0008-5472.CAN-08-0095
20. S. Kauhanen, M. Seppänen, P. Nuutila, Premedication with carbidopa masks positive finding of insulinoma and beta-cell hyperplasia in [(18)F]-dihydroxy-phenyl-alanine positron emission tomography. J. Clin. Oncol. Oncol. **26**, 5307–5308 (2008). https://doi.org/10.1200/JCO.2008.18.8581. author reply5308-5309
21. A. Imperiale, F. Sebag, M. Vix et al. 18F-FDOPA PET/CT imaging of insulinoma revisited. Eur. J. Nucl. Med. Mol. Imaging **42**, 409–418 (2015). https://doi.org/10.1007/s00259-014-2943-z
22. A. Imperiale, T. Bahougne, B. Goichot, P. Bachellier, D. Taïeb, I.J. Namer, Dynamic 18F-FDOPA PET findings after carbidopa premedication in 2 adult patients with insulinoma-related hyperinsulinemic hypoglycemia. Clin. Nucl. Med. **40**, 682–684 (2015). https://doi.org/10.1097/RLU.0000000000000686
23. A. Imperiale, P. Addeo, G. Averous, I.J. Namer, P. Bachellier, Solid pseudopapillary pancreatic tumor mimicking a neuroendocrine neoplasm on ^{18}F-FDOPA PET/CT. J. Clin. Endocrinol. Metab. **98**, 2643–2644 (2013). https://doi.org/10.1210/jc.2013-1942
24. R. Kumar, P. Sharma, P. Garg et al. Role of (68)Ga-DOTATOC PET-CT in the diagnosis and staging of pancreatic neuroendocrine tumours. Eur. Radiol. **21**, 2408–2416 (2011). https://doi.org/10.1007/s00330-011-2199-y
25. C. Schmid-Tannwald, C.M. Schmid-Tannwald, J.N. Morelli et al. Comparison of abdominal MRI with diffusion-weighted imaging to 68Ga-DOTATATE PET/CT in detection of neuroendocrine tumors of the pancreas. Eur. J. Nucl. Med. Mol. Imaging **40**, 897–907 (2013). https://doi.org/10.1007/s00259-013-2371-5
26. P. Sharma, S. Arora, V.S. Dhull et al. Evaluation of (68)Ga-DOTANOC PET/CT imaging in a large exclusive population of pancreatic neuroendocrine tumors. Abdom. Imaging **40**, 299–309 (2015). https://doi.org/10.1007/s00261-014-0219-5
27. P. Sharma, S. Arora, S. Karunanithi et al. Somatostatin receptor based PET/CT imaging with 68Ga-DOTA-Nal3-octreotide for localization of clinically and biochemically suspected insulinoma. Q J. Nucl. Med Mol. Imaging **60**, 69–76 (2016)
28. V. Prasad, A. Sainz-Esteban, R. Arsenic et al. Role of (68)Ga somatostatin receptor PET/CT in the detection of endogenous hyperinsulinaemic focus: an explorative study. Eur. J. Nucl. Med. Mol. Imaging **43**, 1593–1600 (2016). https://doi.org/10.1007/s00259-016-3331-7
29. J. Bertherat, F. Tenenbaum, K. Perlemoine et al. Somatostatin receptors 2 and 5 are the major somatostatin receptors in insulinomas: an in vivo and in vitro study. J. Clin. Endocrinol. Metab. **88**, 5353–5360 (2003). https://doi.org/10.1210/jc.2002-021895
30. Y. Luo, Q. Pan, S. Yao et al. Glucagon-like peptide-1 receptor PET/CT with 68Ga-NOTA-exendin-4 for detecting localized insulinoma: a prospective cohort study. J. Nucl. Med. **57**, 715–720 (2016). https://doi.org/10.2967/jnumed.115.167445
31. E. Christ, D. Wild, S. Ederer et al. Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: a prospective multicentre imaging study. Lancet Diabetes Endocrinol. **1**, 115–122 (2013). https://doi.org/10.1016/S2213-8587(13)70049-4
32. K. Antwi, M. Fani, T. Heye et al. Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: evaluation of diagnostic accuracy in a prospective crossover imaging study. Eur. J. Nucl. Med. Mol. Imaging **45**, 2318–2327 (2018). https://doi.org/10.1007/s00259-018-4101-5
33. A. Haug, C.J. Auernhammer, B. Wängler et al. Intraindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours. Eur. J. Nucl. Med. Mol. Imaging **36**, 765–770 (2009). https://doi.org/10.1007/s00259-008-1030-8
34. D. Putzer, M. Gabriel, D. Kendler et al. Comparison of (68)Ga-DOTA-Tyr(3)-octreotide and (18)F-fluoro-L-dihydroxyphenylalanine positron emission tomography in neuroendocrine tumor patients. Q J. Nucl. Med Mol. Imaging **54**, 68–75 (2010)
35. N. Naswa, P. Sharma, R. Soundararajan et al. Diagnostic performance of somatostatin receptor PET/CT using 68Ga-DOTANOC in gastrinoma patients with negative or equivocal CT findings. Abdom. Imaging **38**, 552–560 (2013). https://doi.org/10.1007/s00261-012-9925-z
36. M. Anlauf, B. Sipos, I. Boeck et al. [Neuroendocrine neoplasms of the distal jejunum and ileum]. Pathology **35**, 283–293 (2014). https://doi.org/10.1007/s00292-013-1888-5. quiz 294
37. S. Balogova, J.-N. Talbot, V. Nataf et al. 18F-fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. Eur. J. Nucl. Med. Mol. Imaging **40**, 943–966 (2013). https://doi.org/10.1007/s00259-013-2342-x
38. K.P. Koopmans, E.G.E. de Vries, I.P. Kema et al. Staging of carcinoid tumours with 18F-DOPA PET: a prospective, diagnostic accuracy study. Lancet Oncol. **7**, 728–734 (2006). https://doi.org/10.1016/S1470-2045(06)70801-4
39. H. Ilhan, W.P. Fendler, C.C. Cyran et al. Impact of (68)Ga-DOTATATE PET/CT on the surgical management of primary neuroendocrine tumors of the pancreas or ileum. Ann. Surg. Oncol. **22**, 164–171 (2015). https://doi.org/10.1245/s10434-014-3981-2
40. V. Ambrosini, P. Tomassetti, P. Castellucci et al. Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours. Eur. J. Nucl. Med. Mol. Imaging **35**, 1431–1438 (2008). https://doi.org/10.1007/s00259-008-0769-2

41. T. Binderup, U. Knigge, A. Loft et al. Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. J. Nucl. Med.**51**, 704–712 (2010). https://doi.org/10.2967/jnumed.109.069765
42. T.H. Tan, C.Y. Boey, B.N. Lee, Impact of 68Ga-DOTA-peptide PET/CT on the management of gastrointestinal neuroendocrine tumour (GI-NET): Malaysian National Referral Centre Experience. Nucl. Med. Mol. Imaging **52**, 119–124 (2018). https://doi.org/10.1007/s13139-017-0496-3
43. T. Belhocine, J. Foidart, P. Rigo et al. Fluorodeoxyglucose positron emission tomography and somatostatin receptor scintigraphy for diagnosing and staging carcinoid tumours: correlations with the pathological indexes p53 and Ki-67. Nucl. Med. Commun. **23**, 727–734 (2002)
44. E. Rust, F. Hubele, E. Marzano et al. Nuclear medicine imaging of gastro-entero-pancreatic neuroendocrine tumors. The key role of cellular differentiation and tumor grade: from theory to clinical practice. Cancer Imaging. **12**, 173–184 (2012). https://doi.org/10.1102/1470-7330.2012.0026
45. R. Abgral, S. Leboulleux, D. Déandreis et al. Performance of (18) fluorodeoxyglucose-positron emission tomography and somatostatin receptor scintigraphy for high Ki67 (≥10%) well-differentiated endocrine carcinoma staging. J. Clin. Endocrinol. Metab. **96**, 665–671 (2011). https://doi.org/10.1210/jc.2010-2022
46. G. Luo, Z. Liu, M. Guo et al. (18)F-FDG PET/CT can be used to detect non-functioning pancreatic neuroendocrine tumors. Int. J. Oncol. **45**, 1531–1536 (2014). https://doi.org/10.3892/ijo.2014.2570
47. S. Partelli, M. Rinzivillo, A. Maurizi et al. The role of combined Ga-DOTANOC and (18)FDG PET/CT in the management of patients with pancreatic neuroendocrine tumors. Neuroendocrinology **100**, 293–299 (2014). https://doi.org/10.1159/000368609
48. E. Garin, F. Le Jeune, A. Devillers et al. Predictive value of 18F-FDG PET and somatostatin receptor scintigraphy in patients with metastatic endocrine tumors. J. Nucl. Med. **50**, 858–864 (2009). https://doi.org/10.2967/jnumed.108.057505
49. M. Bucau, A. Laurent-Bellue, N. Poté et al. 18F-FDG uptake in well-differentiated neuroendocrine tumors correlates with both Ki-67 and VHL pathway inactivation. Neuroendocrinology **106**, 274–282 (2018). https://doi.org/10.1159/000480239
50. E.M. Tabaksblat, S.W. Langer, U. Knigge et al. Diagnosis and treatment of bronchopulmonary neuroendocrine tumours: state of the art. Acta Oncol. Stockh. Swed. **55**, 3–14 (2016). https://doi.org/10.3109/0284186X.2015.1067715
51. B.I. Gustafsson, M. Kidd, A. Chan, M.V. Malfertheiner, I.M. Modlin, Bronchopulmonary neuroendocrine tumors. Cancer **113**, 5–21 (2008). https://doi.org/10.1002/cncr.23542
52. C. Ansquer, D. Taieb, F. Montravers, F. Tenenbaum, PET imaging with 68 gallium labelled somatostatin analogues in the evaluation of neuroendocrine tumours (NETs). http://www.em-consulte.com/en/article/963107. Accessed 16 June 2018.
53. M.F. Bozkurt, I. Virgolini, S. Balogova et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with 68Ga-DOTA-conjugated somatostatin receptor targeting peptides and 18F-DOPA. Eur. J. Nucl. Med. Mol. Imaging **44**, 1588–1601 (2017). https://doi.org/10.1007/s00259-017-3728-y
54. M. Rodrigues, T. Traub-Weidinger, S. Li, B. Ibi, I. Virgolini, Comparison of 111In-DOTA-DPhe1-Tyr3-octreotide and 111In-DOTA-lanreotide scintigraphy and dosimetry in patients with neuroendocrine tumours. Eur. J. Nucl. Med. Mol. Imaging **33**, 532–540 (2006). https://doi.org/10.1007/s00259-005-0020-3
55. V. Ambrosini, P. Castellucci, D. Rubello et al. 68Ga-DOTA-NOC: a new PET tracer for evaluating patients with bronchial carcinoid. Nucl. Med. Commun. **30**, 281–286 (2009). https://doi.org/10.1097/MNM.0b013e32832999c1
56. G. Treglia, P. Castaldi, G. Rindi, A. Giordano, V. Rufini, Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastro-enteropancreatic neuroendocrine tumours: a meta-analysis. Endocrine **42**, 80–87 (2012). https://doi.org/10.1007/s12020-012-9631-1
57. K. Oberg, Molecular imaging radiotherapy: theranostics for personalized patient management of neuroendocrine tumors (NETs). Theranostics **2**, 448–458 (2012). https://doi.org/10.7150/thno.3931
58. I. Kayani, B.G. Conry, A.M. Groves et al. A comparison of 68Ga-DOTATATE and 18F-FDG PET/CT in pulmonary neuroendocrine tumors. J. Nucl. Med. **50**, 1927–1932 (2009). https://doi.org/10.2967/jnumed.109.066639
59. T. Jindal, A. Kumar, B. Venkitaraman et al. Evaluation of the role of [18F]FDG-PET/CT and [68Ga]DOTATOC-PET/CT in differentiating typical and atypical pulmonary carcinoids. Cancer Imaging **11**, 70–75 (2011). https://doi.org/10.1102/1470-7330.2011.0010
60. B. Venkitaraman, S. Karunanithi, A. Kumar, G.C. Khilnani, R. Kumar, Role of 68Ga-DOTATOC PET/CT in initial evaluation of patients with suspected bronchopulmonary carcinoid. Eur. J. Nucl. Med. Mol. Imaging **41**, 856–864 (2014). https://doi.org/10.1007/s00259-013-2659-5
61. N. Pandit, M. Gonen, L. Krug, S.M. Larson, Prognostic value of [18F]FDG-PET imaging in small cell lung cancer. Eur. J. Nucl. Med. Mol. Imaging **30**, 78–84 (2003). https://doi.org/10.1007/s00259-002-0937-8
62. U.-F. Pape, A. Perren, B. Niederle et al. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology **95**, 135–156 (2012). https://doi.org/10.1159/000335629
63. G. Capurso, M. Rinzivillo, R. Bettini, L. Boninsegna, G. Delle Fave, M. Falconi, Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases. Br. J. Surg. **99**, 1480–1486 (2012). https://doi.org/10.1002/bjs.8842
64. M.D. Miljković, M. Girotra, R.R. Abraham, R.B. Erlich, Novel medical therapies of recurrent and metastatic gastro-enteropancreatic neuroendocrine tumors. Dig. Dis. Sci. **57**, 9–18 (2012). https://doi.org/10.1007/s10620-011-1854-0
65. V. Prasad, V. Ambrosini, M. Hommann, D. Hoersch, S. Fanti, R. P. Baum, Detection of unknown primary neuroendocrine tumours (CUP-NET) using (68)Ga-DOTA-NOC receptor PET/CT. Eur. J. Nucl. Med. Mol. Imaging **37**, 67–77 (2010). https://doi.org/10.1007/s00259-009-1205-y
66. N. Naswa, P. Sharma, A. Kumar et al. ^{68}Ga-DOTANOC PET/CT in patients with carcinoma of unknown primary of neuroendocrine origin. Clin. Nucl. Med. **37**, 245–251 (2012). https://doi.org/10.1097/RLU.0b013e31823ea730
67. O. Alonso, M. Rodríguez-Taroco, E. Savio, C. Bentancourt, J.P. Gambini, H. Engler, 68)Ga-DOTATATE PET/CT in the evaluation of patients with neuroendocrine metastatic carcinoma of unknown origin. Ann. Nucl. Med. **28**, 638–645 (2014). https://doi.org/10.1007/s12149-014-0856-3
68. G. Treglia, C. Aktolun, A. Chiti et al. The 2015 Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma: the "evidence-based" refusal to endorse them by EANM due to the "not evidence-based" marginalization of the role of Nuclear Medicine. Eur. J. Nucl. Med. Mol. Imaging **43**, 1486–1490 (2016). https://doi.org/10.1007/s00259-016-3404-7
69. S. Leboulleux, E. Baudin, J.-P. Travagli, M. Schlumberger, Medullary thyroid carcinoma. Clin. Endocrinol. (Oxf.). **61**, 299–310 (2004). https://doi.org/10.1111/j.1365-2265.2004.02037.x

70. A.L. Giraudet, D. Vanel, S. Leboulleux et al. Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. J. Clin. Endocrinol. Metab. **92**, 4185–4190 (2007). https://doi.org/10.1210/jc.2007-1211
71. G. Treglia, P. Castaldi, M.F. Villani et al. Comparison of 18F-DOPA, 18F-FDG and 68Ga-somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma. Eur. J. Nucl. Med. Mol. Imaging **39**, 569–580 (2012). https://doi.org/10.1007/s00259-011-2031-6
72. A.R. Romero-Lluch, J.I. Cuenca-Cuenca, R. Guerrero-Vázquez et al. Diagnostic utility of PET/CT with 18F-DOPA and 18F-FDG in persistent or recurrent medullary thyroid carcinoma: the importance of calcitonin and carcinoembryonic antigen cutoff. Eur. J. Nucl. Med. Mol. Imaging **44**, 2004–2013 (2017). https://doi.org/10.1007/s00259-017-3759-4
73. H.H.G. Verbeek, J.T.M. Plukker, K.P. Koopmans et al. Clinical relevance of 18F-FDG PET and 18F-DOPA PET in recurrent medullary thyroid carcinoma. J. Nucl. Med. **53**, 1863–1871 (2012). https://doi.org/10.2967/jnumed.112.105940
74. F. Caobelli, A. Chiaravalloti, L. Evangelista et al. Predictive and prognostic value of 18F-DOPA PET/CT in patients affected by recurrent medullary carcinoma of the thyroid. Ann. Nucl. Med. **32**, 7–15 (2018). https://doi.org/10.1007/s12149-017-1213-0
75. A. Archier, C. Heimburger, C. Guerin et al. 18)F-DOPA PET/CT in the diagnosis and localization of persistent medullary thyroid carcinoma. Eur. J. Nucl. Med. Mol. Imaging **43**, 1027–1033 (2016). https://doi.org/10.1007/s00259-015-3227-y
76. A. Sesti, M. Mayerhoefer, M. Weber et al. Relevance of calcitonin cut-off in the follow-up of medullary thyroid carcinoma for conventional imaging and 18-fluorine-fluorodihydroxyphenylalanine PET. Anticancer Res. **34**, 6647–6654 (2014)
77. S. Kauhanen, C. Schalin-Jäntti, M. Seppänen et al. Complementary roles of 18F-DOPA PET/CT and 18F-FDG PET/CT in medullary thyroid cancer. J. Nucl. Med. **52**, 1855–1863 (2011). https://doi.org/10.2967/jnumed.111.094771
78. M. Luster, W. Karges, K. Zeich et al. Clinical value of 18-fluorine-fluorodihydroxyphenylalanine positron emission tomography/computed tomography in the follow-up of medullary thyroid carcinoma. Thyroid **20**, 527–533 (2010). https://doi.org/10.1089/thy.2009.0342
79. M.C. Marzola, M.R. Pelizzo, M. Ferdeghini et al. Dual PET/CT with (18)F-DOPA and (18)F-FDG in metastatic medullary thyroid carcinoma and rapidly increasing calcitonin levels: comparison with conventional imaging. Eur. J. Surg. Oncol. **36**, 414–421 (2010). https://doi.org/10.1016/j.ejso.2010.01.001
80. M. Beheshti, S. Pöcher, R. Vali et al. The value of 18F-DOPA PET-CT in patients with medullary thyroid carcinoma: comparison with 18F-FDG PET-CT. Eur. Radiol. **19**, 1425–1434 (2009). https://doi.org/10.1007/s00330-008-1280-7
81. K.P. Koopmans, J.W.B. de Groot, J.T.M. Plukker et al. 18F-dihydroxyphenylalanine PET in patients with biochemical evidence of medullary thyroid cancer: relation to tumor differentiation. J. Nucl. Med. **49**, 524–531 (2008). https://doi.org/10.2967/jnumed.107.047720
82. B. Beuthien-Baumann, A. Strumpf, J. Zessin, J. Bredow, J. Kotzerke, Diagnostic impact of PET with 18F-FDG, 18F-DOPA and 3-O-methyl-6-[18F]fluoro-DOPA in recurrent or metastatic medullary thyroid carcinoma. Eur. J. Nucl. Med. Mol. Imaging **34**, 1604–1609 (2007). https://doi.org/10.1007/s00259-007-0425-2
83. S. Hoegerle, C. Altehoefer, N. Ghanem, I. Brink, E. Moser, E. Nitzsche, 18F-DOPA positron emission tomography for tumour detection in patients with medullary thyroid carcinoma and elevated calcitonin levels. Eur. J. Nucl. Med. **28**, 64–71 (2001)
84. G. Treglia, V. Rufini, M. Salvatori, A. Giordano, L. Giovanella, PET imaging in recurrent medullary thyroid carcinoma. Int. J. Mol. Imaging **2012**, 324686 (2012). https://doi.org/10.1155/2012/324686
85. K. Slavikova, F. Montravers, G. Treglia et al. What is currently the best radiopharmaceutical for the hybrid PET/CT detection of recurrent medullary thyroid carcinoma? Curr. Radiopharm. **6**, 96–105 (2013)
86. M. Soussan, V. Nataf, K. Kerrou et al. Added value of early 18F-FDOPA PET/CT acquisition time in medullary thyroid cancer. Nucl. Med. Commun. **33**, 775–779 (2012). https://doi.org/10.1097/MNM.0b013e3283543304
87. S.A. Wells, S.L. Asa, H. Dralle et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid J. Am. Thyroid Assoc. **25**, 567–610 (2015). https://doi.org/10.1089/thy.2014.0335
88. American Thyroid Association Guidelines Task Force, R.T. Kloos, C. Eng et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid J. Am. Thyroid Assoc. **19**, 565–612 (2009). https://doi.org/10.1089/thy.2008.0403
89. A. Oudoux, P.-Y. Salaun, C. Bournaud et al. Sensitivity and prognostic value of positron emission tomography with F-18-fluorodeoxyglucose and sensitivity of immunoscintigraphy in patients with medullary thyroid carcinoma treated with anticarcinoembryonic antigen-targeted radioimmunotherapy. J. Clin. Endocrinol. Metab. **92**, 4590–4597 (2007). https://doi.org/10.1210/jc.2007-0938
90. J. Barbet, L. Campion, F. Kraeber-Bodéré, J.-F. Chatal; GTE Study Group, Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J. Clin. Endocrinol. Metab. **90**, 6077–6084 (2005). https://doi.org/10.1210/jc.2005-0044
91. K. Pacak, S.H. Tella, *Pheochromocytoma and Paraganglioma*. ed. by L.J. De Groot, G. Chrousos, K. Dungan et al. Endotext. (MDText.com, Inc., South Dartmouth (MA), 2000). http://www.ncbi.nlm.nih.gov/books/NBK481899/. Accessed 12 June 2018.
92. L. Amar, A. Servais, A.-P. Gimenez-Roqueplo, F. Zinzindohoue, G. Chatellier, P.-F. Plouin, Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J. Clin. Endocrinol. Metab. **90**, 2110–2116 (2005). https://doi.org/10.1210/jc.2004-1398
93. R.A. DeLellis, R.V. Lloyd, P.U. Heitz, World Health Organization classification of tumours pathology & genetics. Tumours Endocr. Organs. 151–155 (2004).
94. J. Favier, L. Amar, A.-P. Gimenez-Roqueplo, Paraganglioma and phaeochromocytoma: from genetics to personalized medicine. Nat. Rev. Endocrinol. **11**, 101–111 (2015). https://doi.org/10.1038/nrendo.2014.188
95. D. Taïeb, K. Pacak, Molecular imaging and theranostic approaches in pheochromocytoma and paraganglioma. Cell Tissue Res. **372**, 393–401 (2018). https://doi.org/10.1007/s00441-018-2791-4
96. D. Taïeb, H.J. Timmers, E. Hindié et al., EANM 2012 guidelines for radionuclide imaging of phaeochromocytoma and paraganglioma. Eur. J. Nucl. Med. Mol. Imaging **39**, 1977–1995 (2012). https://doi.org/10.1007/s00259-012-2215-8
97. F. Pacini, M.G. Castagna, L. Brilli, G. Pentheroudakis; ESMO Guidelines Working Group, Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. **23**(Suppl 7), vii110–vii119 (2012). https://doi.org/10.1093/annonc/mds230
98. G. Treglia, F. Cocciolillo, C. de Waure et al. Diagnostic performance of 18F-dihydroxyphenylalanine positron emission tomography in patients with paraganglioma: a meta-analysis. Eur. J. Nucl. Med. Mol. Imaging **39**, 1144–1153 (2012). https://doi.org/10.1007/s00259-012-2087-y
99. S. Hoegerle, N. Ghanem, C. Altehoefer et al. 18F-DOPA positron emission tomography for the detection of glomus tumours.

Eur. J. Nucl. Med. Mol. Imaging **30**, 689–694 (2003). https://doi.org/10.1007/s00259-003-1115-3
100. Timmers HJLM, C.C. Chen, J.A. Carrasquillo et al. Comparison of 18F-fluoro-L-DOPA, 18F-fluoro-deoxyglucose, and 18F-fluorodopamine PET and 123I-MIBG scintigraphy in the localization of pheochromocytoma and paraganglioma. J. Clin. Endocrinol. Metab. **94**, 4757–4767 (2009). https://doi.org/10.1210/jc.2009-1248
101. I. Janssen, C.C. Chen, D. Taieb et al. 68Ga-DOTATATE PET/CT in the localization of head and neck paragangliomas compared with other functional imaging modalities and CT/MRI. J. Nucl. Med. **57**, 186–191 (2016). https://doi.org/10.2967/jnumed.115.161018
102. A. Archier, A. Varoquaux, P. Garrigue et al. Prospective comparison of (68)Ga-DOTATATE and (18)F-FDOPA PET/CT in patients with various pheochromocytomas and paragangliomas with emphasis on sporadic cases. Eur. J. Nucl. Med. Mol. Imaging **43**, 1248–1257 (2016). https://doi.org/10.1007/s00259-015-3268-2
103. A. Kroiss, D. Putzer, A. Frech et al. A retrospective comparison between 68Ga-DOTA-TOC PET/CT and 18F-DOPA PET/CT in patients with extra-adrenal paraganglioma. Eur. J. Nucl. Med. Mol. Imaging **40**, 1800–1808 (2013). https://doi.org/10.1007/s00259-013-2548-y
104. I. Janssen, E.M. Blanchet, K. Adams et al. Superiority of [68Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma. Clin. Cancer Res. **21**, 3888–3895 (2015). https://doi.org/10.1158/1078-0432.CCR-14-2751
105. C. Lepoutre-Lussey, C. Caramella, F. Bidault et al. Screening in asymptomatic SDHx mutation carriers: added value of ^{18}F-FDG PET/CT at initial diagnosis and 1-year follow-up. Eur. J. Nucl. Med. Mol. Imaging **42**, 868–876 (2015). https://doi.org/10.1007/s00259-015-3003-z
106. J.P. Bilezikian, L. Bandeira, A. Khan, N.E. Cusano, Hyperparathyroidism. Lancet Lond. Engl. **391**, 168–178 (2018). https://doi.org/10.1016/S0140-6736(17)31430-7
107. J.P. Bilezikian, M.L. Brandi, R. Eastell et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J. Clin. Endocrinol. Metab. **99**, 3561–3569 (2014). https://doi.org/10.1210/jc.2014-1413
108. A.A. Khan, D.A. Hanley, R. Rizzoli et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporos. Int J. Establ Result Coop. Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA **28**, 1–19 (2017). https://doi.org/10.1007/s00198-016-3716-2
109. A.M. Laird, S.K. Libutti, Minimally invasive parathyroidectomy versus bilateral neck exploration for primary hyperparathyroidism. Surg. Oncol. Clin. N. Am. **25**, 103–118 (2016). https://doi.org/10.1016/j.soc.2015.08.012
110. J.M. Ruda, C.S. Hollenbeak, B.C. Stack, A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol. Head Neck Surg. **132**, 359–372 (2005). https://doi.org/10.1016/j.otohns.2004.10.005
111. C.-Y. Lo, B.H. Lang, W.F. Chan, A.W.C. Kung, K.S.L. Lam, A prospective evaluation of preoperative localization by technetium-99m sestamibi scintigraphy and ultrasonography in primary hyperparathyroidism. Am. J. Surg. **193**, 155–159 (2007). https://doi.org/10.1016/j.amjsurg.2006.04.020
112. C. Ansquer, E. Mirallié, T. Carlier, H. Abbey-Huguenin, F. Aubron, F. Kraeber-Bodéré, Preoperative localization of parathyroid lesions. Value of 99mTc-MIBI tomography and factors influencing detection. Nukl. Nucl. Med. **47**, 158–162 (2008)
113. T. Carlier, A. Oudoux, E. Mirallié et al. 99mTc-MIBI pinhole SPECT in primary hyperparathyroidism: comparison with conventional SPECT, planar scintigraphy and ultrasonography. Eur. J. Nucl. Med. Mol. Imaging **35**, 637–643 (2008). https://doi.org/10.1007/s00259-007-0625-9
114. T. Cazaentre, F. Clivaz, F. Triponez, False-positive result in 18F-fluorocholine PET/CT due to incidental and ectopic parathyroid hyperplasia. Clin. Nucl. Med. **39**, e328–e330 (2014). https://doi.org/10.1097/RLU.0b013e3182a77b62
115. M. Hodolic, V. Huchet, S. Balogova et al. Incidental uptake of (18)F-fluorocholine (FCH) in the head or in the neck of patients with prostate cancer. Radiol. Oncol. **48**, 228–234 (2014). https://doi.org/10.2478/raon-2013-0075
116. P. Mapelli, E. Busnardo, P. Magnani et al. Incidental finding of parathyroid adenoma with 11C-choline PET/CT. Clin. Nucl. Med. **37**, 593–595 (2012). https://doi.org/10.1097/RLU.0b013e31824c5ffc
117. M. Orevi, N. Freedman, E. Mishani, M. Bocher, O. Jacobson, Y. Krausz, Localization of parathyroid adenoma by 11C-choline PET/CT: preliminary results. Clin. Nucl. Med. **39**, 1033–1038 (2014). https://doi.org/10.1097/RLU.0000000000000607
118. L. Lezaic, S. Rep, M.J. Sever, T. Kocjan, M. Hocevar, J. Fettich, ^{18}F-Fluorocholine PET/CT for localization of hyperfunctioning parathyroid tissue in primary hyperparathyroidism: a pilot study. Eur. J. Nucl. Med. Mol. Imaging **41**, 2083–2089 (2014). https://doi.org/10.1007/s00259-014-2837-0
119. M. Hocevar, L. Lezaic, S. Rep et al. Focused parathyroidectomy without intraoperative parathormone testing is safe after preoperative localization with 18F-Fluorocholine PET/CT. Eur. J. Surg. Oncol. J. Eur. Soc. Surg. Oncol. Br. Assoc. Surg. Oncol. **43**, 133–137 (2017). https://doi.org/10.1016/j.ejso.2016.09.016
120. N. Thanseer, S.K. Bhadada, A. Sood et al. Comparative effectiveness of ultrasonography, 99mTc-Sestamibi, and 18F-Fluorocholine PET/CT in detecting parathyroid adenomas in patients with primary hyperparathyroidism. Clin. Nucl. Med. **42**, e491–e497 (2017). https://doi.org/10.1097/RLU.0000000000001845
121. S. Rep, M. Hocevar, J. Vaupotic, U. Zdesar, K. Zaletel, L. Lezaic, 18F-choline PET/CT for parathyroid scintigraphy: significantly lower radiation exposure of patients in comparison to conventional nuclear medicine imaging approaches. J. Radiol. Prot. **38**, 343–356 (2018). https://doi.org/10.1088/1361-6498/aaa86f
122. A.O.J. Bergenfelz, G. Wallin, S. Jansson et al. Results of surgery for sporadic primary hyperparathyroidism in patients with preoperatively negative sestamibi scintigraphy and ultrasound. Langenbecks Arch. Surg. **396**, 83–90 (2011). https://doi.org/10.1007/s00423-010-0724-0
123. B.M. Dy, M.L. Richards, B.J. Vazquez, G.B. Thompson, D.R. Farley, C.S. Grant, Primary hyperparathyroidism and negative Tc99 sestamibi imaging: to operate or not? Ann. Surg. Oncol. **19**, 2272–2278 (2012). https://doi.org/10.1245/s10434-012-2325-3
124. L. Michaud, A. Burgess, V. Huchet et al. Is 18F-fluorocholine-positron emission tomography/computerized tomography a new imaging tool for detecting hyperfunctioning parathyroid glands in primary or secondary hyperparathyroidism? J. Clin. Endocrinol. Metab. **99**, 4531–4536 (2014). https://doi.org/10.1210/jc.2014-2821
125. L. Michaud, S. Balogova, A. Burgess et al. A pilot comparison of 18F-fluorocholine PET/CT, ultrasonography and 123I/99mTc-sestaMIBI dual-phase dual-isotope scintigraphy in the preoperative localization of hyperfunctioning parathyroid glands in primary or secondary hyperparathyroidism: influence of thyroid anomalies. Medicine (Baltimore) **94**, e1701 (2015). https://doi.org/10.1097/MD.0000000000001701
126. S. Grimaldi, J. Young, P. Kamenicky et al., Challenging presurgical localization of hyperfunctioning parathyroid glands in primary hyperparathyroidism: the added value of 18F-Fluorocholine PET/CT. Eur. J. Nucl. Med. Mol. Imaging. (2018). https://doi.org/10.1007/s00259-018-4018-z

127. S. Rep, L. Lezaic, T. Kocjan et al. Optimal scan time for evaluation of parathyroid adenoma with [(18)F]-fluorocholine PET/CT. Radiol. Oncol. **49**, 327–333 (2015). https://doi.org/10.1515/raon-2015-0016
128. W.P. Kluijfhout, W.M.C.M. Vorselaars, S.A.M. van den Berk et al. Fluorine-18 fluorocholine PET-CT localizes hyperparathyroidism in patients with inconclusive conventional imaging: a multicenter study from the Netherlands. Nucl. Med. Commun. **37**, 1246–1252 (2016). https://doi.org/10.1097/MNM.0000000000000595
129. W.P. Kluijfhout, J.D. Pasternak, J.E. Gosnell et al. 18F fluorocholine PET/MR imaging in patients with primary hyperparathyroidism and inconclusive conventional imaging: a prospective pilot study. Radiology **284**, 460–467 (2017). https://doi.org/10.1148/radiol.2016160768
130. E. Quak, D. Blanchard, B. Houdu et al. F18-choline PET/CT guided surgery in primary hyperparathyroidism when ultrasound and MIBI SPECT/CT are negative or inconclusive: the APACH1 study. Eur. J. Nucl. Med. Mol. Imaging **45**, 658–666 (2018). https://doi.org/10.1007/s00259-017-3911-1
131. M. Beheshti, L. Hehenwarter, Z. Paymani et al. 18F-Fluorocholine PET/CT in the assessment of primary hyperparathyroidism compared with 99mTc-MIBI or 99mTc-tetrofosmin SPECT/CT: a prospective dual-centre study in 100 patients. Eur. J. Nucl. Med. Mol. Imaging **45**, 1762–1771 (2018). https://doi.org/10.1007/s00259-018-3980-9
132. S. Fischli, I. Suter-Widmer, B.T. Nguyen et al. The significance of 18F-Fluorocholine-PET/CT as localizing imaging technique in patients with primary hyperparathyroidism and negative conventional imaging. Front. Endocrinol. **8**, 380 (2017). https://doi.org/10.3389/fendo.2017.00380
133. G.F. Huber, M. Hüllner, C. Schmid et al. Benefit of 18F-fluorocholine PET imaging in parathyroid surgery. Eur. Radiol. **28**, 2700–2707 (2018). https://doi.org/10.1007/s00330-017-5190-4
134. C. Amadou, G. Bera, M. Ezziane et al., 18F-Fluorocholine PET/CT and parathyroid 4D computed tomography for primary hyperparathyroidism: the challenge of reoperative patients. World J. Surg. (2019). https://doi.org/10.1007/s00268-019-04910-6
135. O. Koulouri, N. Kandasamy, A.C. Hoole et al. Successful treatment of residual pituitary adenoma in persistent acromegaly following localisation by 11C-methionine PET co-registered with MRI. Eur. J. Endocrinol. **175**, 485–498 (2016). https://doi.org/10.1530/EJE-16-0639