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REVIEW ARTICLE

Diagnostic accuracy of [^{18}F]DOPA PET and PET/CT in patients with neuroendocrine tumors: a meta-analysis

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Abstract The aim of this study was to systematically review and meta-analyze published data on the diagnostic accuracy of positron emission tomography (PET) using fluorine-18-dihydroxyphenylalanine ([^{18}F]DOPA) in patients with neuroendocrine tumors (NETs). A comprehensive computer literature search of the PubMed/MEDLINE, Embase and Scopus databases was conducted to identify studies on the use of [^{18}F]DOPA PET or PET/computed tomography (PET/CT) in patients with proven or suspected NETs. Pooled sensitivity and specificity of [^{18}F]DOPA PET and PET/CT on a per patient-based analysis were calculated. The area under the ROC curve was calculated to measure the accuracy of [^{18}F]DOPA PET or PET/CT. Eight articles on gastroenteropancreatic and thoracic NETs, 13 on pheochromocytoma/paraganglioma (Pheo/PGL) and eight on recurrent medullary thyroid carcinoma (MTC) were included in our meta-analysis. The pooled sensitivity and specificity of [^{18}F]DOPA PET or PET/CT in patients with thoracic and gastroenteropancreatic NETs were 77% (95% CI 71–82) and 95% (95% CI 87–98), respectively. The area under the ROC curve was 0.94. The pooled sensitivity and specificity of [^{18}F]DOPA PET or PET/CT in patients with Pheo/PGL were 92% (95% CI 88–95) and 92% (95% CI 85–97), respectively. The area under the ROC curve was 0.95. The pooled sensitivity of [^{18}F]DOPA PET or PET/CT in patients with recurrent MTC was 62% (95% CI 54–69). Heterogeneity was found between the studies with regard to the sensitivity of [^{18}F]DOPA PET or PET/CT. Evidence-based data show that [^{18}F]DOPA PET and PET/CT are accurate methods in patients with proven or suspected NETs. Large multicenter studies are necessary to substantiate the diagnostic accuracy of [^{18}F]DOPA PET and PET/CT in this setting.

Keywords Positron emission tomography · PET/CT · [^{18}F]DOPA · Neuroendocrine tumors · Paraganglioma · Medullary thyroid carcinoma

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Introduction

Neuroendocrine tumors (NETs) are rare neoplasms that arise from neuroendocrine cells which are present not only in the endocrine glands but also diffusely in all body tissues. Neuroendocrine cells share common features, such as having special secretory granules and often producing biogenic amines and polypeptide hormones. Both normal and tumoral neuroendocrine cells may uptake and decarboxylate amine precursors (such as L-DOPA and 5-hydroxytryptophan) to produce biogenic amines, such as catecholamines and serotonin [1–3].

Although NETs share some pathological and clinical features, significant differences do exist between different tumor types and locations [1–3]. Correct classification of NETs according to the various locations, on the basis of the recently published WHO classification, is important for appropriate treatment in each group [2, 3]. As regards their origin and location, NETs may arise from different regions, such as the gastrointestinal tract, the pancreatic islet cells, the lung and the thymus.

Furthermore, medullary thyroid carcinoma (MTC), arising from parafollicular cells of the thyroid,

pheochromocytoma and paraganglioma (Pheo/PGL), arising from chromaffin cells of the adrenal glands (Pheo) and sympathetic or parasympathetic paraganglia (PGL), are also considered NETs [1].

Functional imaging methods are useful for providing accurate staging and extent of the disease in patients with NETs. Information obtained by combining conventional and functional imaging methods may influence the management of these patients [4, 5].

Recently, the use of positron emission tomography (PET) imaging in NETs has been growing rapidly and different positron-emitting radiopharmaceuticals (with different uptake mechanisms) have been developed [4, 5]. In particular, fluorine-18-dihydroxyphenylalanine ([^{18}F]DOPA) has been proposed as a useful PET tracer for the imaging of NETs, because these tumors have the ability to accumulate and decarboxylate biogenic amines such as L-DOPA [6]. After intracellular uptake through the large amino acid transporter, [^{18}F]DOPA is decarboxylated by DOPA decarboxylase to [^{18}F]DOPAmine, which is transported into storage granules by vesicular monoamine transporter and trapped intracellularly [6].

Several single-center studies have evaluated the diagnostic performance of [^{18}F]DOPA PET or PET/CT in patients with proven or suspected NETs, reporting different values of sensitivity and specificity; the purpose of our article is to systematically review and meta-analyze published data on the diagnostic accuracy of [^{18}F]DOPA PET or PET/CT in patients with NETs, in order to add more evidence-based data in this setting.

Methods

Search strategy

A comprehensive computer literature search of the PubMed/MEDLINE, Embase and Scopus databases was conducted to find published articles on the diagnostic performance of [^{18}F]DOPA PET and PET/CT in patients with NETs, including patients with gastroenteropancreatic and thoracic NETs, Pheo/PGL, neuroblastoma, MTC, and ectopic adrenocorticotropin-secreting tumors. We used a search algorithm that was based on a combination of the terms: (a) "DOPA" or "dihydroxyphenylalanine" and (b) "PET" or "positron emission tomography". No start date limit was used; the search was updated till 23 October 2012. No language restriction was used. To expand our search, references of the retrieved articles were also screened for additional studies.

Study selection

Studies (or subsets in studies) investigating the diagnostic accuracy of [^{18}F]DOPA PET or PET/CT in patients with NETs were eligible for inclusion. The exclusion criteria were: (a) articles not within the field of interest of this review; (b) review articles, editorials or letters, comments, conference proceedings; (c) case reports or small case series; (d) overlap of patient data (in such cases the most complete article was included); (e) insufficient data to calculate sensitivity or specificity from individual studies on a per patient-based analysis.

Two researchers (VR and GT) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. Articles were rejected if they were clearly ineligible. The same two researchers then independently reviewed the full-text versions of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data extraction

For each included study, information was collected concerning the basic study (authors, journal, year of publication, country of origin, study design), patient characteristics (population evaluated, number of patients performing PET, mean age, sex), other functional imaging performed and technical aspects (device used, [^{18}F]DOPA injected dose, time between [^{18}F]DOPA injection and image acquisition, carbidopa pretreatment, image analysis, applied reference standard). For each study, the numbers of true-positive, false-positive, true-negative and false-negative findings for [^{18}F]DOPA PET or PET/CT on a per patient-based analysis were recorded.

Quality assessment

Two independent reviewers evaluated the methodology of the selected studies using QUADAS, a tool for the quality assessment of diagnostic accuracy studies [7].

Statistical analysis

Sensitivity and specificity of [^{18}F]DOPA PET or PET/CT in patients with NETs were obtained on a per patient-based analysis from individual studies. A random effect model was used for statistical pooling of the data taking into account heterogeneity between the studies. Pooled data were presented with 95% confidence intervals (95% CI). An I^2 statistic was also performed to test for heterogeneity between studies. The area under the ROC curve was calculated to measure the accuracy of [^{18}F]DOPA PET or PET/CT in patients with NETs. Statistical analyses were performed using Meta-DiSc statistical software version 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain) [8].

Results

Literature search

The comprehensive computer literature search of the PubMed/MEDLINE, Embase and Scopus databases revealed 1,218 articles. On reviewing the titles and abstracts, 1,166 articles were excluded as case reports, reviews, editorials or articles not within the field of interest of this review.

Fifty-two articles were selected and retrieved in full-text version; no additional study was found on screening the references of these articles. The full texts of these 52 articles potentially eligible for inclusion were then reviewed and four were excluded as case series, eight because of possible data overlap and nine due to insufficient data to calculate sensitivity or specificity of [^{18}F]DOPA PET. The number of retrieved articles dealing with neuroblastoma [9, 10] and ectopic adrenocorticotropin-secreting tumors [11] was not sufficient to perform a meta-analysis.

Finally, eight articles on gastroenteropancreatic and thoracic NETs, 13 on Pheo/PGL and eight on recurrent MTC met all the inclusion and none of the exclusion criteria, and were included in our meta-analysis [12–39] (Fig. 1). The characteristics of the included studies are presented in Tables 1, 2, 3, 4, 5, and 6.

Quality assessment

Overall, the studies included in this systematic review showed moderate methodological quality, as assessed using QUADAS. The studies scored between 7/14 and 11/14 with a median score of 9/14. The index test and the reference standard were often interpreted without blinding, and this was the most critical issue with regard to the methodological quality of the included studies.

Diagnostic performance

The diagnostic performance results of [^{18}F]DOPA PET or PET/CT in the included studies were divided into three groups.

The sensitivity and specificity of [^{18}F]DOPA PET or PET/CT in patients with thoracic and gastroenteropancreatic NETs ranged from 56 to 95% and from 89 to 100%, with pooled estimates of 77% (95% CI 71–82) and 95% (95% CI 87–98), respectively (Fig. 2a, b). The included studies were statistically quite heterogeneous in their estimates of sensitivity (I^2 61%) and homogeneous in their estimates of specificity (I^2 0%). The area under the ROC curve was 0.94 (Fig. 2c).

The sensitivity and specificity of [^{18}F]DOPA PET or PET/CT in patients with Pheo/PGL ranged from 77 to 100% and from 75 to 100%, with pooled estimates of 92% (95% CI 88–95) and 92% (95% CI 85–97), respectively (Fig. 3a, b). The included studies were statistically quite heterogeneous in their estimates of sensitivity (I^2 52.7%) and homogeneous in their estimates of specificity (I^2 0%). The area under the ROC curve was 0.95 (Fig. 3c).

The sensitivity of [^{18}F]DOPA PET or PET/CT in patients with recurrent MTC ranged from 44 to 83% with

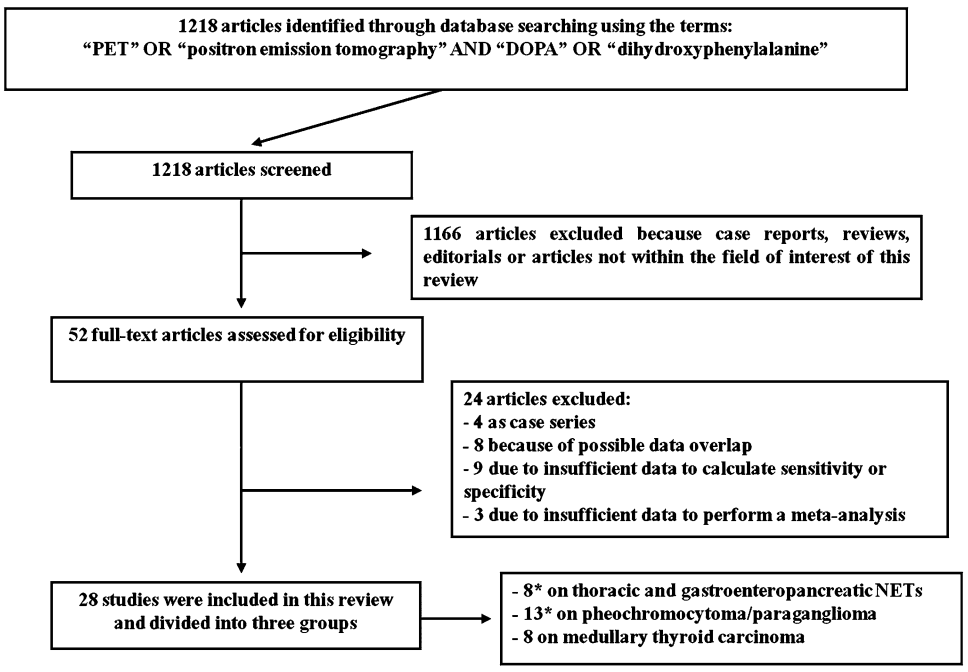

Fig. 1 Flow chart of the search for eligible studies on the diagnostic accuracy of [^{18}F]DOPA PET and PET/CT in patients with NETs

Table 1 Basic study data and patient characteristics from the included studies that used [^{18}F]DOPA PET or PET/CT in thoracic and gastroenteropancreatic NETs

References	Country	Study design	Population	Patients performing [^{18}F]DOPA PET or PET/CT	Mean age (years)	%Male	Type of NETs evaluated	Other functional imaging performed
Hoegerle et al. [12]	Germany	NR	Patients with GI-NET	17	55	59	17GI	^{18}F-FDG-PET, SRS
Koopmans et al. [13]	Netherlands	Prospective	Patients with known or suspected NET	47	56	62	24GI + T, 23P	SRS, ^{11}C-5-HTP-PET
Ambrosini et al. [14]	Italy	Prospective	Patients with known or suspected NET	13	63	54	3GI, 2T, 8P	^{68}Ga-DOTANOC-PET
Haug et al. [15]	Germany	NR	Patients with known NET	25	57	64	9GI, 6T, 5P, 1O, 4UP	^{68}Ga-DOTATATE-PET
Kauhanen et al. [16]	Finland	Retrospective	Patients with known or suspected NET	39[a]	NR	NR	26GI, 13P	–
Montravers et al. [17]	France	NR	Patients with known or suspected NET	69 (90 scans)	NR	NR	22GI, 22P, 25UP	–
Schiesser et al. [18]	Switzerland	Prospective	Patients with known or suspected NET	52[a]	59	46	7GI, 9P, 36UP	SRS
Yakemchuk et al. [19]	Canada	Prospective	Patients with known or suspected NET	27	56	44	19GI, 2P, 6UP	SRS

NR not reported, *GI* gastrointestinal, *T* thoracic, *P* pancreatic, *UP* unknown primary, *O* other, *SRS* somatostatin receptor scintigraphy, *^{18}F-FDG* fluorine-18-fluorodeoxyglucose, *^{11}C-5-HTP* carbon-11-5-hydroxytryptophan, *^{68}Ga-DOTANOC* and *^{68}Ga-DOTATATE* Gallium-68-somatostatin analogs

[a] Only patients with thoracic and gastroenteropancreatic NETs were included

pooled estimates of 62% (95% CI 54–69) (Fig. 4). The included studies were statistically quite heterogeneous in their estimates of sensitivity (I^2 49.2%). The pooled specificity of [^{18}F]DOPA PET or PET/CT in patients with recurrent MTC could not be calculated from the included studies due to lack of data on false-positive and true-negative findings.

Discussion

Several single-center studies have used [^{18}F]DOPA PET or PET/CT in patients with proven or suspected NETs, reporting different values of sensitivity and specificity [12–39]. However, many of these studies have limited power, analyzing only relatively small numbers of patients. In order to derive more robust estimates of the diagnostic accuracy of [^{18}F]DOPA PET or PET/CT in this setting, we pooled published studies, adopting a systematic review process to identify studies.

Overall, the studies included in this meta-analysis showed moderate quality according to QUADAS [7]. However, this tool has some limitations given that it is not meant to be used as a scale. In fact, the items have different relevance in the assessment of quality: the quality of a study achieving a very high score, with almost all the items fulfilled, could still be debatable if it does not meet one of the most important items, such as the use of the same reference standard in all the patients. Another drawback of QUADAS is that it does not take into consideration sample size, which determines the precision of the study and its validity too. On the other hand, it is important to remember that the low quality could also be due to limitations in carrying out these kinds of studies in the real clinical setting, where it might be difficult to confirm the final diagnosis in all patients.

The pooled results of our meta-analysis indicate that [^{18}F]DOPA PET and PET/CT are accurate diagnostic methods in patients with thoracic and gastroenteropancreatic NETs (the area under the ROC curve was 0.94), demonstrating a good pooled specificity (95%) and a moderate sensitivity (77%).

Nevertheless, possible sources of false-negative results of these functional imaging methods should be kept in mind; these could be related to several factors, such as small size of the neuroendocrine lesion, location of the tumor near organs with high physiological [^{18}F]DOPA uptake (such as the pancreas, biliary and urinary systems),

Table 2 Technical aspects of the included studies that used [^{18}F]DOPA PET or PET/CT for detecting thoracic and gastroenteropancreatic NETs

References	Device	[^{18}F]DOPA mean injected dose	Time between [^{18}F]DOPA injection and image acquisition (min)	Carbidopa pretreatment	Image analysis	Reference standard
Hoegerle et al. [12]	PET	200 ± 30 MBq	60–90	No	Visual	Histology and/or clinical/imaging follow-up
Koopmans et al. [13]	PET and PET/CT	180 ± 50 MBq	60	Yes	Visual	Histology and/or clinical/imaging follow-up
Ambrosini et al. [14]	PET/CT	370 MBq	60	No	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Haug et al. [15]	PET/CT	360 MBq	60	No	Visual and semiquantitative	Imaging
Kauhanen et al. [16]	PET/CT	234 ± 56 MBq	60	Yes	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Montravers et al. [17]	PET or PET/CT	2–5 MBq/kg	60	No	Visual	Histology and/or clinical/imaging follow-up
Schiesser et al. [18]	PET/CT	200–220 MBq	45	No	Visual	Histology and/or clinical/imaging follow-up
Yakemchuk et al. [19]	PET/CT	201 ± 12 MBq	60	No	Visual	Histology and/or clinical/imaging follow-up

or loss of [^{18}F]DOPA uptake due to tumor dedifferentiation.

The sensitivity of these methods could also be related to the location and type of NET. [^{18}F]DOPA PET and PET/CT have a very high sensitivity in midgut NETs, much better than the pooled value of 77%, but a low sensitivity in foregut NETs (including bronchial, gastric, duodenal and pancreatic NETs) [40]. In some articles, patients with NETs were divided into two populations (carcinoid and non-carcinoid tumors). A higher sensitivity of [^{18}F]DOPA PET and PET/CT in patients with carcinoid tumors compared to non-carcinoid tumors (i.e. pancreatic NETs) was reported [13, 17, 40].

The high specificity of [^{18}F]DOPA PET and PET/CT in patients with NETs can be explained by the fact that only neuroendocrine cells are able to take up, decarboxylate, and store amino acids and their amines. With regard to this high specificity, an important advantage over other PET tracers (such as Gallium-68-somatostatin analogs and fluorine-18-fluorodeoxyglucose) is that [^{18}F]DOPA is not taken up in a significant proportion by inflammatory cells.

The pooled results of our meta-analysis indicate that [^{18}F]DOPA PET and PET/CT are accurate diagnostic methods in patients with Pheo/PGL (the area under the ROC curve was 0.95), demonstrating a good pooled specificity (92%) and sensitivity (92%). The possible sources of false-negative results are the ones previously mentioned. Furthermore, discordant results regarding the influence of genetic factors in the diagnostic accuracy of these methods are reported. Timmers et al. [25] reported that succinate dehydrogenase B (SDHB) gene mutations may result in extra-adrenal PGLs which, compared with non-SDHB-related lesions, show a lower sensitivity of [^{18}F]DOPA PET. Recently, Rischke et al. [31] reported that [^{18}F]DOPA PET is a sensitive and specific imaging modality for the detection and staging of Pheo/PGL in various genotypes, including SDHD-mutation carriers, and in patients with no germline mutation.

According to the literature data, [^{18}F]DOPA PET and PET/CT seem to be accurate methods in both adrenal and extra-adrenal, sympathetic and parasympathetic, functioning and non-functioning, and metastatic and non-metastatic Pheo/PGL [16, 20–31]. In particular, [^{18}F]DOPA PET and PET/CT seem to be the most sensitive imaging methods for detecting head and neck PGLs, usually parasympathetic-derived tumors, probably because of the high tracer avidity of these neoplasms and the favorable lesion-to-background ratio in the head and neck [21, 30].

Evidence-based data from our meta-analysis suggest that [^{18}F]DOPA PET and PET/CT are associated with a moderate sensitivity in the evaluation of recurrent MTC (62%). On the other hand, this pooled sensitivity should be considered significant, because [^{18}F]DOPA PET and PET/CT are often performed in patients with suspected recurrent MTC after negative findings on conventional imaging studies. In fact, in most cases, patients are referred for [^{18}F]DOPA PET or PET/CT because of rising levels of calcitonin, a very sensitive and specific tumor marker for

Table 3 Basic study data and patient characteristics from the included studies that used [^{18}F]DOPA PET or PET/CT in patients with pheochromocytoma or paraganglioma

References	Country	Study design	Population	Patients with suspected PGL performing [^{18}F]DOPA PET or PET/CT	Mean age (years)	%Male	Patients with genetic mutation	Other functional imaging performed
Hoegerle et al. [20]	Germany	NR	Patients with suspected PGL	14	44	64	5 VHL	MIBG
Hoegerle et al. [21]	Germany	NR	Patients with SDHD mutations (suspected PGL)	10	44	60	10 SDHD	–
Taïeb et al. [22]	France	Retrospective	Patients with known PGL	9	51	89	1 SDHB, 1 SDHD, 2 VHL	^{18}F-FDG, MIBG, SRS
Kauhanen et al. [16]	Finland	Retrospective	Patients with known or suspected PGL	25	40	45	NR	MIBG, SRS
Imani et al. [23]	USA	Retrospective	Patients with suspected PGL	25	51	36	2 SDHB, 1 VHL	–
Fiebrich et al. [24]	Netherlands	Prospective	Patients with suspected PGL	48	46	42	7 MEN, 2 SDHB, 1 SDHD, 3 VHL, 2 NF1	MIBG
Timmers et al. [25]	USA	Prospective	Patients with known or suspected PGL	52	47	54	22 SDHB, 4 SDHD, 3 MEN, 2 VHL	^{18}F-FDG, ^{18}F-FDA, MIBG
Luster et al. [26]	Germany	Retrospective	Patients with suspected PGL	25	45	36	12 MEN	–
Fottner et al. [27]	Germany	Prospective	Patients with suspected PGL	30	42	47	2 MEN, 2 SDHB, 6 SDHD, 1 VHL, 2 NF1	MIBG
Charrier et al. [28]	France	Prospective	Patients with known or suspected extra-adrenal PGL	40	NR	80	5 SDHB, 2 SDHD, 1 VHL	SRS
Rufini et al. [29]	Italy	Retrospective	Patients with known or suspected recurrent PGL	12	47	50	NR	MIBG
King et al. [30]	USA	Prospective	Patients with head and neck PGL	10	38	90	7 SDHD, 3 SDHB	^{18}F-FDG, ^{18}F-FDA, MIBG, SRS
Rischke et al. [31]	Germany	Retrospective	Patients with known or suspected PGL	101	45	55	1 MEN, 20 SDHB, 2 SDHC, 11 SDHD, 19 VHL, 1 NF1	–

PGL paraganglioma, *NR* not reported, *MEN* multiple endocrine neoplasia, *SDHB* succinate dehydrogenase B, *SDHC* succinate dehydrogenase C, *SDHD* succinate dehydrogenase D, *NF1* neurofibromatosis type 1, *VHL* von Hippel Lindau, *MIBG* radiolabeled metaiodobenzylguanidine, *SRS* somatostatin receptor scintigraphy, *^{18}F-FDG* fluorine-18-fluorodeoxyglucose, *^{18}F-FDA* fluorine-18-fluorodopamine

Table 4 Technical aspects of the included studies that used [^{18}F]DOPA PET or PET/CT for detecting pheochromocytoma or paraganglioma

References	Device	[^{18}F]DOPA mean injected dose	Time between [^{18}F]DOPA injection and image acquisition (min)	Carbidopa pretreatment	Image analysis	Reference standard
Hoegerle et al. [20]	PET	220 MBq	90	No	Visual	MRI
Hoegerle et al. [21]	PET	247 MBq	90	No	Visual	MRI
Taïeb et al. [22]	PET or PET/CT	285 MBq	60	No	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Kauhanen et al. [16]	PET or PET/CT	234 MBq	60	Yes, in some cases	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Imani et al. [23]	PET or PET/CT	471 MBq	60	Yes, in some cases	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Fiebrich et al. [24]	PET	180 MBq	60	Yes	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Timmers et al. [25]	PET	460 MBq	30	Yes	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Luster et al. [26]	PET/CT	309 MBq	60	Yes	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Fottner et al. [27]	PET	238 MBq	60–80	No	Visual	Histology and/or clinical/imaging follow-up
Charrier et al. [28]	PET/CT	4 MBq/kg	60–90	No	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Rufini et al. [29]	PET/CT	4 MBq/kg	60	No	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
King et al. [30]	PET	444 MBq	30	Yes	Visual	Imaging
Rischke et al. [31]	PET or PET/CT	286 MBq	47 ± 18	No	Visual and semiquantitative	Histology and/or clinical/imaging follow-up

MTC, in a context of occult biochemical recurrence where all the other imaging modalities have failed. In this context, a sensitivity of over 50% means a successful modality.

Furthermore, [^{18}F]DOPA PET and PET/CT may affect the management of a significant number of patients with recurrent MTC [32–39, 41].

Possible causes of false-negative results of [^{18}F]DOPA PET and PET/CT could be related to small MTC lesions or to dedifferentiation. Furthermore, according to the literature data, the sensitivity of these methods in detecting recurrent MTC increases in patients with higher calcitonin levels and lower calcitonin doubling times [41].

This meta-analysis had some limitations related to possible publication bias and heterogeneity between the studies. Publication bias is a major concern in all forms of pooled analysis, because studies reporting significant findings are more likely to be published than those reporting non-significant results. Indeed, it is not unusual for small-sized early studies to report positive relationships that subsequent larger studies fail to replicate. We cannot exclude a publication bias in our analysis, but we tried to minimize such a bias by excluding case reports and small case series from the analysis.

Heterogeneity between studies may be a potential source of bias; the studies included were statistically heterogeneous in their estimates of sensitivity but homogeneous with regard to specificity. Because systematic reviews bring together studies that are different both clinically and methodologically, heterogeneity in their results is to be expected. For example, heterogeneity is likely to arise through diversity in methodological aspects, study quality, inclusion criteria and differences between the patients included. However, such variability was accounted for in the random effect model.

As regards the methodological heterogeneity between the included studies, some authors used carbidopa pretreatment before [^{18}F]DOPA PET examination; this drug, decreasing decarboxylation and subsequent renal clearance of DOPA, may be used to increase the tumor-to-background uptake ratio in patients with NETs [42].

Table 5 Basic study data and patient characteristics from the included studies that used [^{18}F]DOPA PET or PET/CT in patients with recurrent medullary thyroid carcinoma

References	Country	Study design	Population	MTC patients performing [^{18}F]DOPA PET or PET/CT	Mean age (years)	%Male	Other functional imaging performed
Hoegerle et al. [32]	Austria	Prospective	Patients with suspected recurrent MTC	10[a]	57	55	^{18}F-FDG, SRS
Beuthien-Baumann et al. [33]	Germany	Retrospective	Patients with suspected recurrent MTC	15	56	53	^{18}F-FDG, ^{18}F-OMFD
Beheshti et al. [34]	Austria	Prospective	Patients with suspected recurrent MTC	19[a]	59	38	^{18}F-FDG
Marzola et al. [35]	Italy	NR	Patients with suspected recurrent MTC	18	51	44	^{18}F-FDG
Luster et al. [36]	Germany	Retrospective	Patients with suspected recurrent MTC	26 (28 scans)	48	46	–
Kauhanen et al. [37]	Finland	Prospective	Patients with suspected recurrent MTC	19	52	53	^{18}F-FDG
Treglia et al. [38]	Italy	Retrospective	Patients with suspected recurrent MTC	18	53	33	^{18}F-FDG, ^{68}Ga-SMS
Verbeek et al. [39]	Netherlands	Retrospective	Patients with suspected recurrent MTC	36	52	47	^{18}F-FDG

MTC medullary thyroid carcinoma, *NR* not reported, *^{18}F-FDG* fluorine-18-fluorodeoxyglucose, *SRS* somatostatin receptor scintigraphy, *^{18}F-OMFD* fluorine-18-methyl-fluoro-DOPA, *^{68}Ga-SMS* Gallium-68-somatostatin analogs

[a] Patients evaluated before surgery were excluded from the analysis

Table 6 Technical aspects of the included studies that used [^{18}F]DOPA PET or PET/CT for detecting recurrent medullary thyroid carcinoma

References	Device	Mean [^{18}F]DOPA injected activity	Time between [^{18}F]DOPA injection and image acquisition (min)	Carbidopa	Image analysis	Reference standard
Hoegerle et al. [32]	PET	220 MBq	90	No	Qualitative	Histology and/or clinical/imaging follow-up
Beuthien-Baumann et al. [33]	PET	4.8 MBq/kg	45	Yes	Qualitative	Histology and/or clinical/imaging follow-up
Beheshti et al. [34]	PET/CT	4 MBq/kg	30	No	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Marzola et al. [35]	PET/CT	2.2 MBq/kg	60	No	Qualitative and semiquantitative	Histology
Luster et al. [36]	PET/CT	298 MBq	60	Yes	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Kauhanen et al. [37]	PET/CT	243 MBq	60	Yes	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up
Treglia et al. [38]	PET/CT	4 MBq/kg	60	No	Qualitative	Histology and/or clinical/imaging follow-up
Verbeek et al. [39]	PET/CT	200 MBq	60	Yes	Qualitative and semiquantitative	Histology and/or clinical/imaging follow-up

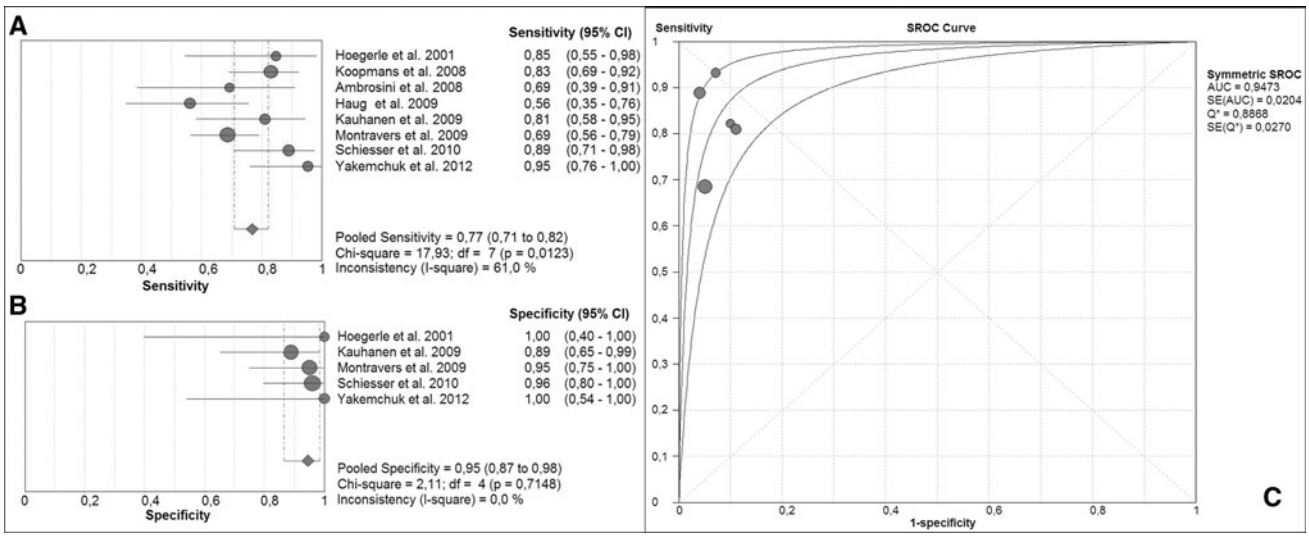

Fig. 2 Plot of individual studies and pooled sensitivity (**a**) and specificity (**b**) of [^{18}F]DOPA PET and PET/CT in patients with thoracic and gastroenteropancreatic NETs on a per patient-based analysis. The size of the *circles* indicates the weight of each study. Pooled sensitivity and specificity were 77% (95% CI 71–82) and 95% (95% CI 87–98), respectively. Summary ROC curve of diagnostic accuracy of [^{18}F]DOPA PET and PET/CT in patients with thoracic and gastroenteropancreatic NETs on a per patient-based analysis (**c**). The area under the ROC curve was 0.94

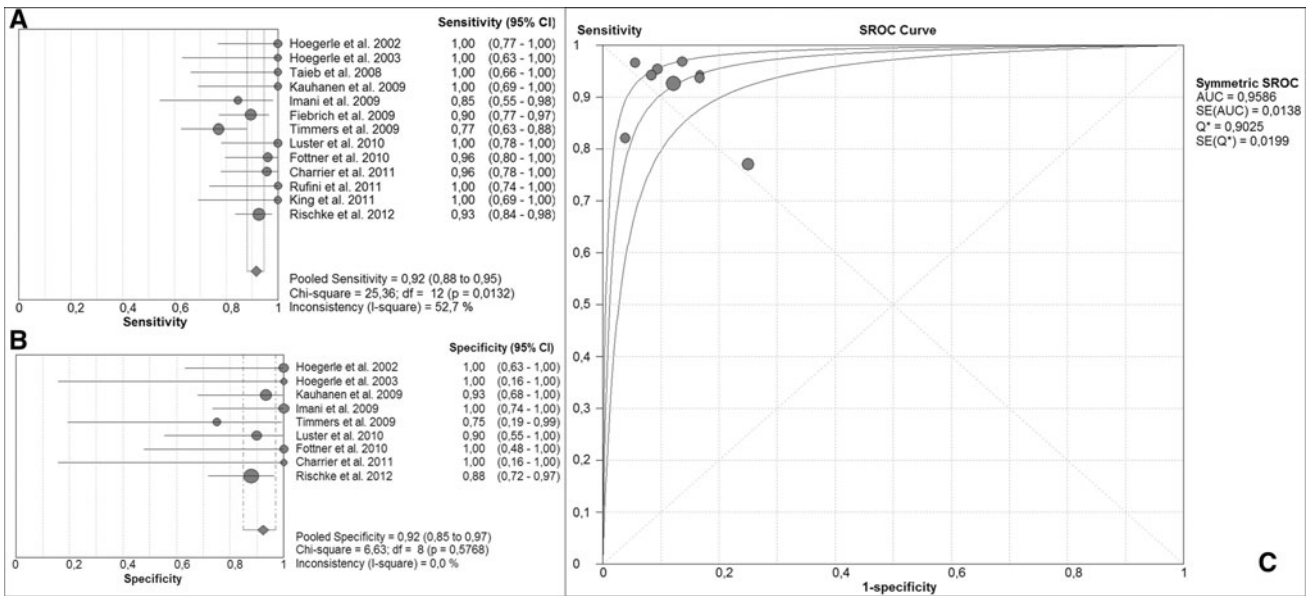

Fig. 3 Plot of individual studies and pooled sensitivity (**a**) and specificity (**b**) of [^{18}F]DOPA PET and PET/CT in patients with Pheo/PGL on a per patient-based analysis. The size of the *circles* indicates the weight of each study. Pooled sensitivity and specificity were 92% (95% CI 88–95%) and 92% (95% CI 85–97%), respectively. Summary ROC curve of diagnostic accuracy of [^{18}F]DOPA PET and PET/CT in patients with Pheo/PGL on a per patient-based analysis (**c**). The area under the ROC curve was 0.95

Hybrid PET/CT imaging is usually superior to PET alone in terms of diagnostic accuracy of tumor imaging; our analysis did not evaluate a possible advantage of PET/CT versus PET alone because the numbers were too small to allow the detection of a significant difference. Furthermore, some studies performed both PET and PET/CT and separate data could not be retrieved.

At present, besides [^{18}F]DOPA PET/CT, the most widely used PET technique for NET imaging is somatostatin receptor (SSR) PET/CT using Gallium-68-somatostatin analogs (DOTA-NOC, DOTA-TOC or DOTA-TATE), which shows high diagnostic accuracy in this setting, as demonstrated by a recent meta-analysis [43]; in fact, the use of F-18-FDG should be limited to poorly differentiated

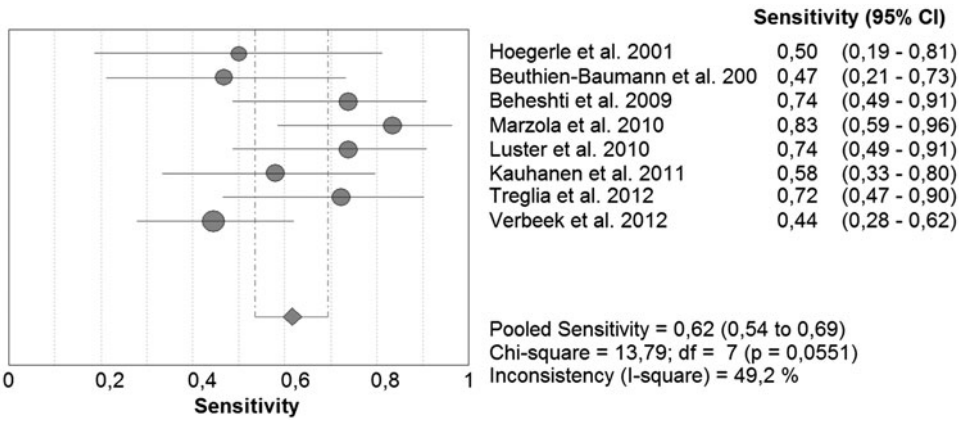

Fig. 4 Plot of individual studies and pooled sensitivity of [^{18}F]DOPA PET and PET/CT in patients with recurrent MTC on a per patient-based analysis. The size of the *circles* indicates the weight of each study. Pooled sensitivity was 62% (95% CI 54–69)

tumors [4, 44, 45]. The real problem for the physician is how to select an appropriate radiopharmaceutical in clinical practice. [^{18}F]DOPA and Gallium-68-somatostatin analogs selectively depict different functional characteristics of neuroendocrine cells; thus, for well-differentiated NETs, the decision should be guided by the biology of NETs. The peculiar features of NETs, taking up and decarboxylating L-DOPA and transforming it into dopamine, make [^{18}F]DOPA particularly suited to visualizing tumors with high metabolic activity such as Pheo/PGL and carcinoid tumors with elevated serotonin levels. In the case of Gallium-68-somatostatin analogs, the receptor-based uptake mechanism allows NET lesions to be visualized independently of their functional activity. Moreover, Gallium-68-somatostatin analogs allow patients to be selected prior to peptide receptor radionuclide therapy. The few studies comparing SSR and [^{18}F]DOPA PET/CT in patients with gastroenteropancreatic and thoracic NETs showed an overall superiority of SSR PET/CT compared to [^{18}F]DOPA [14, 15, 46]. Nevertheless, separate comparison studies taking into account the different location of gastroenteropancreatic and thoracic NETs are needed to confirm the superiority of SSR PET/CT over [^{18}F]DOPA in this setting.

To date, there are no significant data on the comparison of SSR and [^{18}F]DOPA PET/CT in patients with Pheo/PGL; instead, there is one study comparing SSR and [^{18}F]DOPA PET/CT in patients with recurrent MTC, which showed the superiority of [^{18}F]DOPA over SSR PET/CT in this setting [38]. More head-to-head comparison studies between SSR and [^{18}F]DOPA PET/CT are needed to address the choice of PET radiopharmaceuticals for evaluating NETs in clinical practice.

Conclusions

Evidence-based data from our analysis show that [^{18}F]DOPA PET and PET/CT are accurate methods in patients with proven or suspected NETs, taking into account the histological type of NET and the clinical setting. Large prospective multicenter studies are necessary to substantiate the diagnostic accuracy of [^{18}F]DOPA PET and PET/CT in the different types of NETs.

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Conflict of interest None.

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