Head-to-head comparison between F-18-DOPA PET/CT and Ga-68-DOTA-peptide PET/CT in detecting intestinal neuroendocrine tumours

Piccardo, Arnoldo; Fiz, Francesco; Bottoni, Gianluca; Ugolini, Martina; Noordzij, Walter; Trimboli, Pierpaolo

Published in:
Clinical Endocrinology

DOI:
10.1111/cen.14527

Received: 28 April 2021 | Revised: 12 May 2021 | Accepted: 18 May 2021

DOI: 10.1111/cen.14527

ORIGINAL ARTICLE

WILEY

Head-to-head comparison between ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT in detecting intestinal neuroendocrine tumours: A systematic review and meta-analysis

Arnoldo Piccardo[1] | Francesco Fiz[1,2] | Gianluca Bottoni[1] | Martina Ugolini[1] | Walter Noordzij[3] | Pierpaolo Trimboli[4,5]

[1]Nuclear Medicine Department, Ente Ospedaliero "Ospedali Galliera", Genoa, Italy

[2]Humanitas Research Hospital - IRCCS, Rozzano, Italy

[3]Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

[4]Faculty of Biomedical Sciences, Università della Svizzera Italiana (USI), Lugano, Switzerland

[5]Clinic of Endocrinology and Diabetology, Lugano and Mendrisio Regional Hospital, Ente Ospedaliero Cantonale, Bellinzona, Switzerland

Correspondence
Arnoldo Piccardo, Department of Nuclear Medicine, E.O. Ospedali Galliera, Mura delle Cappuccine 14, 16128 Genoa, Italy.
Email: arnoldo.piccardo@galliera.it

Abstract

Objective: The imaging of intestinal neuroendocrine tumours (NETs) relies on functional PET tracers; these tumours can be studied by means of both ^{68}Ga-DOTA-peptides and ^{18}F-DOPA PET/CT. As yet, it is unclear which of these two modalities offers the better sensitivity. We therefore conducted a meta-analysis to assess the available data.

Design: PubMed, CENTRAL, Scopus and Web of Science were searched for studies comparing the sensitivity of ^{68}Ga-DOTA-peptides and ^{18}F-DOPA PET/CT; papers up to February 2021 were considered.

Patients and Measurements: In each study, we considered sensitivity in terms of patient-based (PBA), region-based (RBA) and lesion-based analysis (LBA) and pooled the results yielded by each tracer. Multidisciplinary follow-up served as the standard of truth.

Results: Of the 636 records identified, 6 articles published between 2008 and 2021 were finally selected, and 112 intestinal NET patients were included. The pooled sensitivity of ^{18}F-DOPA PET/CT was 83%, 89% and 95% on PBA, RBA and LBA, respectively. ^{68}Ga-DOTA peptide PET/CT showed sensitivity of 88%, 92% and 82% on PBA, RBA and LBA, respectively. No significant differences were found between the two tracers on PBA and RBA. By contrast, a clear trend towards significance in favour of ^{18}F-DOPA PET/CT was identified on LBA. The presence of a significant difference in favour of ^{18}F-DOPA PET/CT was confirmed in a subgroup analysis conducted only on the most recent and largest studies. In all three analyses, mild-to-high heterogeneity was found, while no publication bias was observed.

Conclusion: Both ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT are reliable diagnostic procedures in patients with intestinal NETs. However, in terms of lesion detection, a non-negligible difference in favour of ^{18}F-DOPA PET/CT was observed. Thus, the use of ^{18}F-DOPA PET/CT could be considered as a first-line molecular procedure in intestinal NETs.

Arnoldo Piccardo and Pierpaolo Trimboli share co-authorship.

KEYWORDS
^{18}F-DOPA, ^{68}Ga-DOTA, meta-analysis, neuroendocrine, PET/CT

1 | INTRODUCTION

Neuroendocrine tumours (NETs) are a very heterogeneous group of neoplasms originating from the neural crest and arising from various organs throughout the body. These tumours differ in their biological behaviour and aggressiveness, but have common functional characteristics.

The gastrointestinal tract is one of the main sites of origin of NETs, which can produce various peptides and neurotransmitters. From a clinical point of view, these neoplasms could be silent or cause symptoms related to tumour invasion or hormone secretion. The principal distant metastatic locations are liver and bone and even at this advanced stage, NET patients have relatively long overall survival.[1] From genetic point of view, intestinal NETs present distinct gene mutations, which set them apart from pancreatic NETs, as well as from aggressive neuroendocrine carcinomas. These alterations, which include activation of the PI3K/mTOR, MAP-Kinase and Wnt pathways, inconstant mutations of CDKN1 and APC, and chromosomal aberrations,[2] may represent viable therapeutic targets.[3] Moreover, these tumours express specific receptors, thereby providing potential targets for molecular imaging procedures. On the one hand, NETs may express high levels of somatostatin receptors (SSTRs), which can be detected by somatostatin analogues (^{68}Ga-DOTA-peptides) PET/CT.[4,5] On the other, NET cells can often take up and decarboxylate monoamine precursors, such as dihydroxyphenylalanine (DOPA), which reflects the secretory activity of these tumours. This functional mechanism can therefore be easily revealed by ^{18}F-fluorodihydroxyphenyl-L-alanine (^{18}F-DOPA).[6] Indeed, owing to the heterogeneity and functional peculiarity of NETs, selecting the proper PET tracer for each NET may be challenging, even when only the gastrointestinal tract is considered.[6] Well-differentiated jejuno-intestinal (midgut) tumours are a well-recognized subgroup of NETs and originate from enterochromaffin cells of the small intestine. Although these tumours may be small, they tend to metastasize to local-regional lymph nodes and the liver. In addition, the presence of many liver metastases is associated with a higher risk of developing carcinoid syndrome (eg flushing, diarrhoea and bronchoconstriction) due to the overproduction of serotonin.[6] Given that surgery with radical intent has a high impact on prognosis, even in the case of liver metastases,[7,8] accurate imaging procedures for staging are required, in order to select the most appropriate surgical approach.

Although well-differentiated midgut tumours often over-express somatostatin receptor (SSTR) type 2, and ^{68}Ga-DOTA-peptides have been recognized as very sensitive imaging biomarkers in these neoplasms,[9] a growing body of evidence seems to indicate a pivotal role of ^{18}F-DOPA as an imaging tracer that can accurately identify the metastatic burden of patients affected by this NET subtype.[10–12] To date, however, there are no solid and conclusive evidence-based data on the comparison of ^{68}Ga-DOTA-peptide PET/CT and ^{18}F-DOPA PET/CT in this particular setting of patients. Thus, whether we should use ^{68}Ga-DOTA-peptide PET/CT rather than ^{18}F-DOPA PET/CT for this purpose is still unknown. Furthermore, recent EANM procedural guidelines[9] suggested both tracers as first-choice diagnostic procedures in patients affected by midgut NETs. However, in a recent letter from Imperiale et al.,[13] the authors pointed out that ^{18}F-DOPA PET/CT can be considered the first-choice tracer in the intestinal tract by considering its specific uptake mechanism and its more favourable biodistribution in the bowel and liver.

Given this clinical and technical background, we systematically searched the literature for original papers reporting the head-to-head comparison of these two imaging procedures in the detection of disease in patients affected by intestinal NETs. We also conducted a meta-analysis of the available data in terms of diagnostic performance (ie detection rate and sensitivity).

2 | MATERIALS AND METHODS

2.1 | Review

The systematic review was conducted in accordance with the PRISMA statement.[14]

2.2 | Search strategy

A four-step search strategy was adopted, and the literature search was performed independently by two of the authors (AP and PT). Firstly, sentinel studies were sought in PubMed by using multiple combinations of the following keywords: ^{18}F-DOPA, ^{68}Ga-DOTA-peptides, radiolabelled somatostatin analogues, PET/CT and neuroendocrine tumours. Secondly, keywords and MeSH terms were identified in PubMed. Thirdly, PubMed, CENTRAL, Scopus and Web of Science were searched. Fourthly, we examined studies that compared the ability of ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT in detecting neuroendocrine tumours (ie PubMed/MEDLINE, Embase and Web of Science). The last search was performed on 1 March 2021. To identify additional studies and expand our search, the references of the articles retrieved were also screened. Studies based on preclinical data, phantom studies, case reports and studies with overlapping data were excluded. All initially eligible articles were screened, and those reporting a head-to-head comparison of ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT in NET patients were included. The patients included in the studies were considered in the analysis only if they had undergone both studies and were affected by intestinal NETs.

2.3 | Data extraction

The following information was extracted independently and in duplicate by two investigators (AP and PT) in a piloted form: (1) general characteristics of the studies (authors, year of publication, country, study type, number of patients); (2) technical aspects (imaging modality used, fasting before radiotracer injection and premedication, mean radiotracer activity injected, time interval between radiotracer injection and image acquisition, time between the two procedures, PET/CT scan extension, PET/CT image analysis and other imaging methods performed for comparison); (3) sensitivity of the imaging procedure on a per patient-based analysis (PBA) calculated in all intestinal NETs patients; (4) sensitivity of the imaging procedure on a per region-based analysis (RBA) and on a per lesion-based analysis (LBA) calculated in patients after adequate multidisciplinary follow-up; and (5) standard of reference (SOR). For data extraction, full papers and supplementary data were searched; if data were missing, the authors were contacted via email. Data were cross-checked, and any discrepancy was discussed through an online consensus meeting.

2.4 | Study quality assessment

The risk of bias of the studies included was assessed independently by two reviewers (AP and PT) by means of the QUADAS-2 tool. In accordance with the QUADAS-2 recommendations,[15] the risk of bias was rated as low, high or unclear. A bias score was calculated, in which every instance of high bias counted as one point and every instance of unclear bias was rated as 0.5 points; studies were excluded if they totalled 4 points or more across the seven QUADAS-2 sub-domains.

2.5 | Statistical analysis

A proportion meta-analysis was performed by implementing a random-effects statistical model. Pooled data were presented with 95% confidence interval (95% CI) values. Heterogeneity among studies was assessed by means of the I-square statistic (I^2), with 50% or higher being regarded as high. Publication bias was evaluated by means of Egger's test.[16] Multidisciplinary follow-up was adopted as SOR to calculate the sensitivity of the two imaging modalities on PBA, RBA and LBA. The StatsDirect statistical software version 3.2.109 (StatsDirect Ltd.) was used for the statistical analyses.

3 | RESULTS

3.1 | Literature search

A total of 636 records were identified after duplicate removal, and their titles and abstracts were analysed; 100 articles were excluded because they were case reports. Of the remaining 536 records, 530 were excluded because they did not meet the inclusion criteria (see Figure 1 for details). Therefore, 6 articles were finally selected, and 112 intestinal NET patients were included (Figure 1).[17–22]

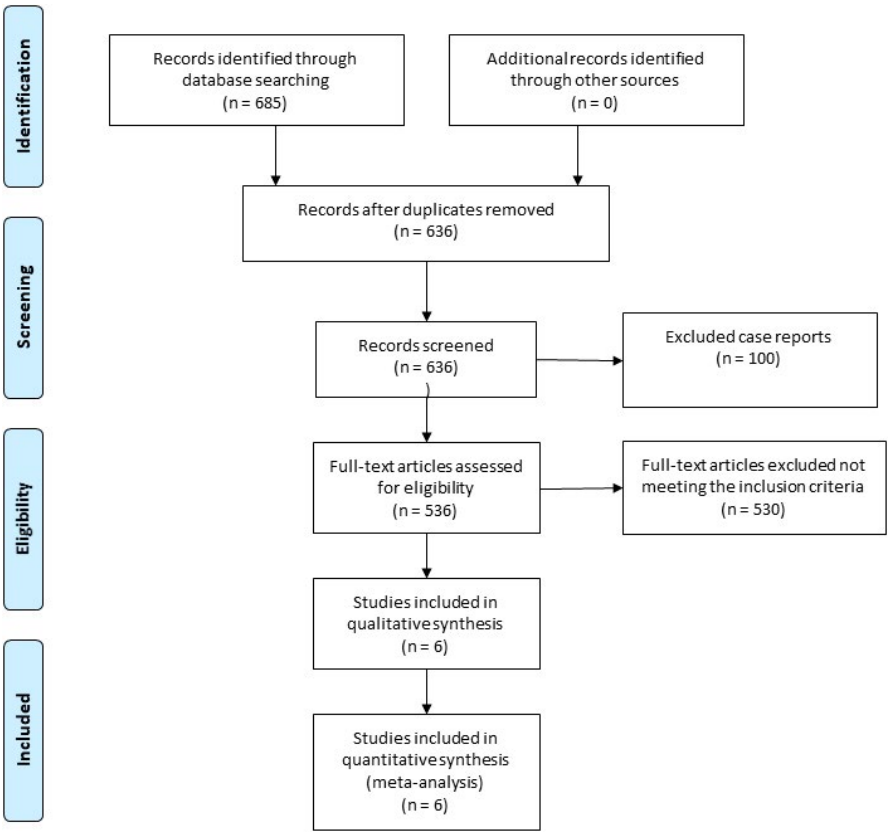

FIGURE 1 PRISMA flow chart, detailing the studies' selection process

3.2 | Qualitative analysis (Systematic review)

The six articles included in the systematic review were published between 2008 and 2021. All studies had a retrospective design. Two studies were carried out in France, while Italy, Germany, Austria and the Netherlands contributed one study each. The characteristics of the studies and patients are summarized in Table 1.

3.2.1 | Technical aspects

The imaging modality was a low-dose PET/CT in four of the six studies.[17,18,21,22] In one of the other 2, a PET stand-alone imaging modality was adopted,[19] while in the remaining one, contrast-enhanced and low-dose PET/CT were performed.[22]

Information on fasting and premedication with carbidopa before radiotracer injection were not available in all articles. The mean injected radiotracer activity ranged from 200 to 370 MBq for ^{18}F-DOPA and from 120 to 200 for ^{68}Ga-DOTA-peptides. The time interval between radiotracer injection and PET/CT image acquisition was similar across the studies, being 60 min for both tracers in the majority of cases. PET image analysis was performed by means of qualitative (visual) analysis and, in all but one study, additional semi-quantitative analysis through the calculation of the maximal standardized uptake values (SUVmax). On visual analysis, all foci of radiotracer uptake greater than the surrounding tissue that could not be explained by physiological activity were considered to be abnormal in 4 studies.[17,18,20,22] In the remaining two studies, PET findings were defined as positive in the case of tracer uptake higher than physiological activity.[19,21] All technical aspects are summarized in Table 2.

3.2.2 | Main findings

The six articles included in the systematic review were published between 2008 and 2021 and had sample sizes ranging from 13 to 45 patients with clinical evidence of NETs. The number of patients with intestinal NETs ranged from 2 to 41 (Table 1).

Table 3 details the available data from all studies included in the present systematic review. Overall, ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT performed well in detecting patients with intestinal NET localizations, identifying more than 80% of true-positive patients.[17–22] However, discrepancies between the two imaging modalities were observed in the three oldest studies, which enrolled only 14 patients with intestinal NETs,[17–19] the anatomical origin of which (ie foregut, midgut or hindgut) was not clearly specified.[18] In these studies, ^{68}Ga-DOTA-peptide PET/CT correctly identified all 14 positive patients (100%), while ^{18}F-DOPA PET/CT identified 9/14 (64%).[17–19] However, when patients with high levels of serotonin were considered, ^{18}F-DOPA PET/CT had the same diagnostic performance as ^{68}Ga-DOTA-peptide PET/CT[18]. By contrast, in the three most recent and largest studies,

TABLE 1 Study and patient characteristics

Authors	Year	Country	Study Design	Total number of patients included in the study	Patients with intestinal NETs included in the study	Well-differentiated/poor differentiated tumours/not defined	Staging/restaging	Patients with high levels of tumour markers (serotonin or 5-HIAA)	Standard of reference (SOR)
Ambrosini et al.[13]	2008	Italy	Retrospective	13	3	3/0/0	3	NR	Multidisciplinary*
Ansquer et al.[18]	2021	France	Retrospective	30	30	26/0/4	9/21	NR	Multidisciplinary*
Haug et al.[14]	2009	Germany	Retrospective	25	9	9/0/0	9/0	9 (serotonin)	Multidisciplinary*
Ouvrard et al.[16]	2020	France	Retrospective	41	41	41/0/0	0/41	9 (5-HIAA)	Multidisciplinary*
Putzer et al.[15]	2010	Austria	Retrospective	15	2	NR	2/0	NR	Multidisciplinary*
Veenstra et al.[17]	2021	Netherland	Retrospective	45	27	27/0/0	NR	22 (serotonin) and 19 (5-HIAA)	Multidisciplinary*

Abbreviation: NR, not reported.

TABLE 2 Technical aspects of PET imaging in the included studies

Authors	Radiotracer	Hybrid imaging modality	PET/CT tomograph	Patient preparation	Mean radiotracer injected activity	Time interval between radiotracer injection and image acquisition	Timeframe between the two PET/CT	Image analysis
Ambrosini et al.[13]	^{18}F-DOPA and ^{68}Ga-DOTANOC	PET/CT with low-dose CT	Discovery LS (General Electric)	fasting (6h)	^{18}F-DOPA: 370 MBq ^{68}Ga-DOTANOC:185MBq	60 min for both tracers	Up to 30 days	visual and semi-quantitative (SUV_{max})
Ansquer et al.[18]	^{18}F-DOPA and ^{68}Ga-DOTANOC	PET/CT with low-dose CT	Biograph mCT 40 or 64 (Siemens)	NR	^{18}F-DOPA: 210 MBq ^{68}Ga-DOTANOC:150MBq	60 min for both tracers	Median 33 days	visual and semi-quantitative (SUV_{max} and SUVratio)
Haug et al.[14]	^{18}F-DOPA and ^{68}Ga-DOTATATE	PET/CT with low-dose CT and contrast-enhanced CT	Gemini (Philips) or Biograph TruePoint (Siemens)	NR	^{18}F-DOPA: 360 MBq ^{68}Ga-DOTATATE:200 MBq	60 min for both tracers	Median 42 days	visual and semi-quantitative (SUV_{max})
Ouvrard et al.[16]	^{18}F-DOPA and ^{68}Ga-DOTATOC	PET/CT with low-dose CT	Biograph128 mCT (Siemens), Vereos, (Philips) pr Discovery 710 (General Electric)	NR	^{18}F-DOPA: 3-4 MBq/kg ^{68}Ga-DOTATOC:2-3 MBq/kg	30 min for ^{18}F-DOPA 60 min for ^{68}Ga-DOTATOC	Up to 3 months	visual
Putzer et al.[15]	^{18}F-DOPA and ^{68}Ga-DOTATOC	PET only	Advance (General Electric)	NR	^{18}F-DOPA:370 MBq ^{68}Ga-DOTATOC:150 MBq	60 min for ^{18}F-DOPA 60-90 min for ^{68}Ga-DOTATOC	NR	visual and semi-quantitative (SUV_{max})
Veenstra et al.[17]	^{18}F-DOPA and ^{68}Ga-DOTATOC	PET/CT with low-dose CT and contrast-enhanced CT	Biograph mCT 40 or 64 (Siemens)	fasting (6h for ^{18}F-DOPA and 1h for ^{68}Ga-DOTATOC) and carbidopa premedication (before ^{18}F-DOPA injection)	^{18}F-DOPA:200 MBq ^{68}Ga-DOTATOC:120 MBq	60 min for both tracers	Up to 6 months	visual and semi-quantitative (SUV_{max})

Abbreviations: CT, computed tomography; MBq, MegaBecquerel; NR, not reported; PET/CT, positron emission tomography; SUV_{max}, maximal standardized uptake value SUVratio, lesion to background uptake ratio.

TABLE 3 Data available in the six studies included in the present systematic review

First author [ref]	Patients	^{18}F-DOPA PET/CT	^{68}Ga-DOTA-peptide PET/CT	Regions	^{18}F-DOPA PET/CT	^{68}Ga-DOTA-peptide PET/CT	Lesions	^{18}F-DOPA PET/CT	^{68}Ga-DOTA-peptide PET/CT
	n (tot)	+ve	−ve	n (tot)	+ve	−ve	n (tot)	+ve	−ve
Ambrosini[13]	3	2	3	4	3	4	16	11	16
Ansquer[18]	30	27	25	81	77	71	221	211	195
Haug[14]	9	5	9	20	13	20	NA	NA	NA
Ouvrard[16]	41	32	32	73	69	64	605	580	483
Putzer[15]	2	2	2	NA	NA	NA	NA	NA	NA
Veenstra[17]	27	26	26	11	11	11	466	465	249

Abbreviation: NA, not available.

TABLE 4 Quality assessment of the studies and risk of bias in each study considered

		Risk of bias				Feasibility		
First author	Year	Patient selection	Study test	Reference standard	Timing	Patient selection	Study test	Reference standard
Ambrosini et al.[13]	2008	L	L	L	L	L	L	L
Ansquer et al.[18]	2021	L	U	L	L	L	L	L
Haug et al.[14]	2009	H	L	L	L	H	L	L
Ouvrard et al.[16]	2020	L	H	L	L	L	L	L
Putzer et al.[15]	2010	U	L	L	U	H	L	L
Veenstra et al.[17]	2021	L	U	L	U	L	L	L

Abbreviation: H, high; L, low; U, unclear.

TABLE 5 Pooled sensitivity for PBA, RBA and LBA of ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT

	PBA			RBA			LBA		
	Sensitivity (95% CI)	I^2 (%)	Egger test (p)	Sensitivity (95% CI)	I^2 (%)	Egger test (p)	Sensitivity (95% CI)	I^2 (%)	Egger test (p)
^{18}F-DOPA PET/CT	0.83 (0.70 to 0.92)	51.4	0.2435	0.89 (0.78 to 0.97)	71.2	0.2545	0.95 (0.89 to 0.99)	92.8	0.0924
^{68}Ga-DOTA-peptide PET/CT	0.88 (0.79 to 0.94)	29.7	0.8664	0.92 (0.85 to 0.96)	38	0.4798	0.82 (0.63 to 0.94)	97.8	0.8143

Abbreviation: PBA, patient-based analysis; RBA, region-based analysis; LBA, lesion-based analysis

which enrolled a more homogeneous series, with 98 patients affected by well-differentiated intestinal NETs (84% of their entire population), a good diagnostic concordance between the two different modalities was found in terms of PBA.[20–22] However, ^{18}F-DOPA PET/CT detected a significantly higher number of lesions than ^{68}Ga-DOTA-peptide PET/CT.[20–22] Overall, the difference in sensitivity between the two imaging modalities ranged from 7% to 46% in favour of ^{18}F-DOPA PET/CT,[20–22] which was able to detect up to 86% more lesions than ^{68}Ga-DOTA-peptide PET/CT.[21] This higher diagnostic performance was observed especially in the case of liver[20,22] and bone metastases,[22] and in patients with G2 tumours rather than in those with G1 tumours.[21] Particularly, ^{18}F-DOPA PET/CT was more sensitive than ^{68}Ga-DOTA-peptide PET/CT in patients with high levels of tumour markers (ie serotonin and 5-hydroxyindoleacetic acid).[21,22]

3.3 | Quality assessment of the studies

The risk of bias was assessed according to four study characteristics; these results are reported in Table 4. In general, the risk of bias ranged from low to high. Specifically, patient selection bias was unclear in one of the six studies and high in another. Importantly, the SOR was appropriate in evaluating sensitivity (ie multidisciplinary follow-up) in all studies. As the mean QUADAS-2 score ranged from 0 to 2, no study had to be excluded because of an elevated risk of bias.

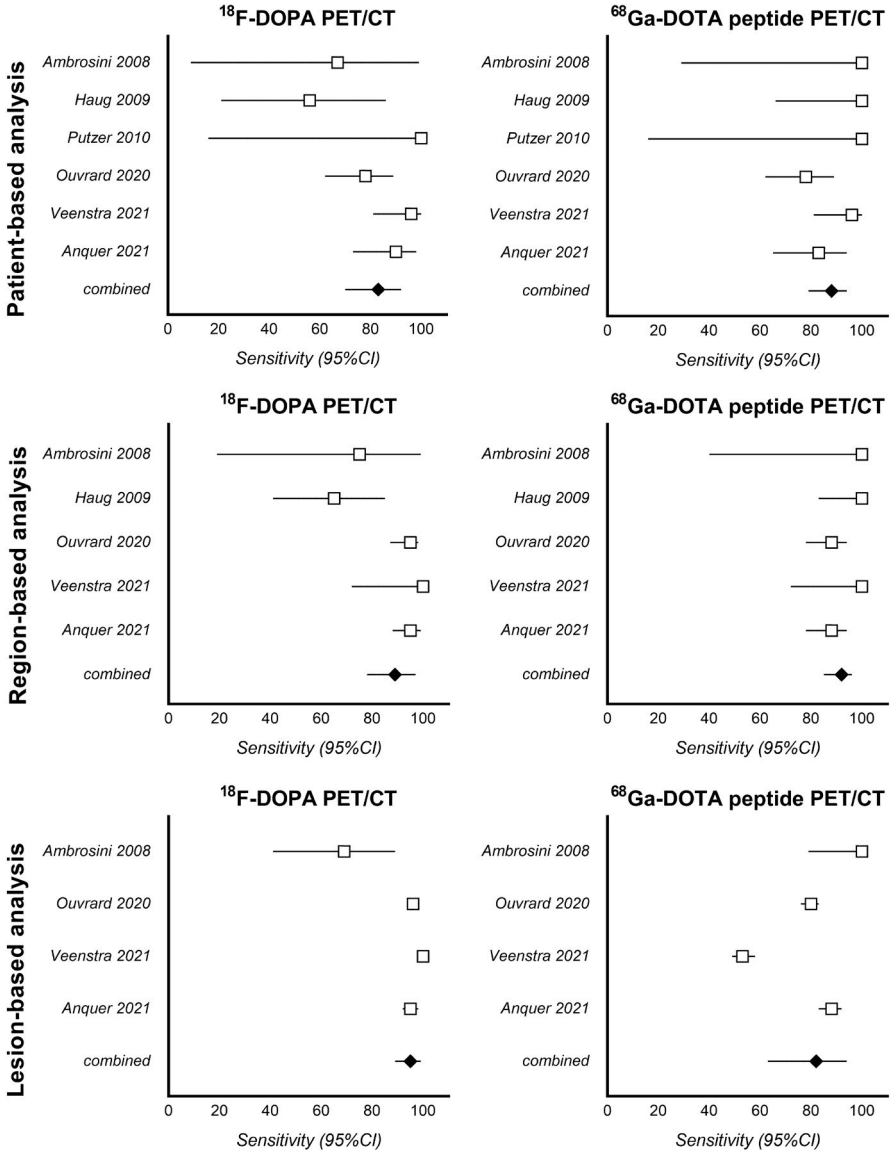

FIGURE 2 Forest plot displaying the pooled sensitivity of the included studies according to the patient-based (top panels), region-based (middle panels) and lesion-based analysis

TABLE 6 Heterogeneity exploration considering two groups of studies

	PBA		RBA		LBA	
	Sensitivity (95% CI)	I_2 (%)	Sensitivity (95% CI)	I_2 (%)	Sensitivity (95% CI)	I_2 (%)
^{18}F-DOPA PET/CT—older studies [13–15]	0.64 (0.39 to 0.85)	0	0.65 (0.46 to 0.82)[*,a]	0	NA	NA
^{18}F-DOPA PET/CT—recent studies [16–18]	0.87 (0.75 to 0.96)	58.7	0.95 (0.91 to 0.97)[*]	0	0.97 (0.93 to 1.00)[#]	93
^{68}Ga-DOTA-peptide PET/CT—older studies [13–15]	0.96 (0.81 to 1.00)	0	0.98 (0.90 to 1.00)[a]	0	NA	NA
^{68}Ga-DOTA-peptide PET/CT—recent studies [16–18]	0.85 (0.73 to 0.94)	58.5	0.88 (0.83 to 0.93)	3.2	0.75 (0.54 to 0.91)[#]	98.4

Note: Please note that PBA could be calculated on six studies, RBA on five and LBA on four.

Abbreviation: PBA, patient-based analysis; RBA, region-based analysis; LBA, lesion-based analysis.

[a]significant difference between ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT.

*significant difference between older and more recent studies.

3.4 | Quantitative analysis (Meta-analysis)

The pooled sensitivity of ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT in terms of PBA, RBA and LBA was calculated (Table 5 and Figure 2) according to the available data (see Table 3). Regarding PBA, the pooled sensitivity of ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT was 83 and 88%, respectively. In the RBA, the pooled sensitivity of ^{18}F-DOPA PET/CT was 89% and that of ^{68}Ga-DOTA-peptide PET/CT 92%. In the LBA, by contrast, the pooled sensitivity of ^{18}F-DOPA PET/CT was higher than that of ^{68}Ga-DOTA-peptide PET/CT (95% vs. 82%). In all three analyses, mild-to-high heterogeneity was found, while no publication bias was observed (Table 5).

On the basis of the above results, the heterogeneity of PBA, RBA and LBA was explored. The timing of the studies, their sample sizes, the prevalence of intestinal NETs and the value of circulating markers (ie serotonin and 5-HIAA) were considered in this analysis. However, this last variable was excluded, since the scant data did not allow accurate exploration. Since full concordance of the data was found in the other three variables, we considered the following two groups: (1) older studies, smaller series and low prevalence of intestinal NETs[17–19]; and (2) more recent studies, larger series and high prevalence of intestinal NETs.[20–22] As illustrated in Table 6, the heterogeneity of ^{18}F-DOPA PET/CT results disappeared from the RBA when we considered these two groups. In this secondary analysis, the pooled sensitivity of ^{18}F-DOPA PET/CT recorded in the set of more recent studies was significantly higher than that recorded in the group of older studies in the RBA. Moreover, on LBA, the pooled sensitivity of ^{18}F-DOPA PET/CT recorded in the group of more recent studies was significantly higher than that of ^{68}Ga-DOTA-peptide PET/CT. The pooled sensitivity of ^{68}Ga-DOTA-peptide PET/CT recorded in the group of older studies was significantly higher than that of ^{18}F-DOPA PET/CT on RBA.

4 | DISCUSSION

The aim of this systematic review and meta-analysis was to produce evidence-based data on the comparative diagnostic ability of ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT in patients affected by intestinal NETs. By using a proper qualitative and quantitative analysis that included only intestinal NET patients, we demonstrated that there were no significant differences in sensitivity between the two tracers at the patient- and region-based levels. Indeed, both molecular imaging modalities proved able to detect patients and body regions with NETs metastases with similarly high sensitivity. The absence of difference between the two modalities can, however, be explained by the overall balance that emerged from the apparently conflicting data. On the one hand, the data from inhomogeneous NET populations reported by the three oldest and smallest studies, which included patients with unspecified *gut* tumours,[17–19] showed that ^{68}Ga-DOTA-peptides performed better than ^{18}F-DOPA. On the other hand, the data from the three largest and most recent studies, which analysed a homogeneous population of well-differentiated intestinal NET patients (the majority had *midgut* tumours), demonstrated that ^{18}F-DOPA performed better than ^{68}Ga-DOTA-peptides.[20–22]

It is worth highlighting that, in the LBA, ^{18}F-DOPA PET/CT was more sensitive than ^{68}Ga-DOTA-peptides, and a trend towards significance was observed in our quantitative analysis. Indeed, two of the three largest studies, which included 71 of the 112 patients in our analysis, reported a significant difference in favour of ^{18}F-DOPA PET/CT in terms of lesion identification[20-22]. This finding, as was recognized by the authors,[20–22] was particularly evident in patients affected by well-differentiated ileal NETs and in the presence of high levels of serotonin or 5-HIIA.[21,22] Therefore, in this context, the evidence-based data support the EANM recommendation[9] to use ^{18}F-DOPA as the PET tracer of choice. However, if this is not available, ^{68}Ga-DOTA-peptides are an effective alternative.

Although the studies included in this analysis did not evaluate the impact on clinical management of the diagnostic superiority of one imaging procedure over another, some considerations should be taken into account when an exclusively diagnostic ^{68}Ga-DOTA-peptides approach is proposed. First, patients with well-differentiated ileal NETs benefit from a surgical approach with a curative intent.[7,8,20] In this setting, a more sensitive imaging modality, like ^{18}F-DOPA PET/CT, could better disclose additional loco-regional and liver metastases, thus guiding a radical surgical procedure. Second, although the advantage of ^{68}Ga-DOTA-peptides over the other diagnostic modalities lies in the theranostic implications of these tracers, especially in advanced disease, it is as yet unclear to what extent data from this modality are able to predict the response to peptides receptor radionuclide therapy (PRRT). The most recent data suggest that predictive factors in this context are the results of the fluorodeoxyglucose PET and a Ki67 score below 20%.[23] Heterogeneity between ^{68}Ga-DOTA and ^{18}F-DOPA uptake could be considered an additional contributing factor in determining PRRT effectiveness.

Until recently, ^{68}Ga-DOTA-peptide PET/CT was considered sensitive enough to be used in all NET forms. However, as we found here, ^{18}F-DOPA PET/CT has recently gained momentum owing to its high reliability in the setting of intestinal NETs. The data presented in this meta-analysis match the information provided by Rufini and colleagues, which focused on the diagnostic accuracy of ^{18}F-DOPA PET and PET/CT in various clinical settings, and found, at the patient-based analysis, a very high sensitivity for ^{18}F-DOPA PET/CT for gastroenteropancreatic NETs.[24] Accordingly, ^{18}F-DOPA PET/CT could be considered in the diagnostic pathway of patients affected by well-differentiated ileal NET metastases and scheduled for peptide receptor radionuclide therapy (PRRT). The available data suggest that the predominance of ^{18}F-DOPA-positive, ^{68}Ga-DOTA-negative lesions is found in specific cases, such as well-differentiated midgut tumours and increased circulating markers: in these cases, ^{18}F-DOPA PET could be worth considering as the main examination when staging candidates for potentially curative surgery and as an adjunct in the case of PRRT evaluation. Thus, these results indicate a

NET-adapted diagnostic strategy that includes using ^{18}F-DOPA PET/CT for intestinal tumours.

The limitations and strengths of our systematic review and meta-analysis should also be mentioned. First, only six studies, involving a relatively small number of patients, were included in this meta-analysis. Moreover, all six had a retrospective design, and three included a low number of intestinal NET patients.

In addition, information on RBA and LBA was available only in five and four studies, respectively. However, the stringent selection criteria, which only allowed the inclusion of studies reporting a head-to-head evaluation of ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT performed on the same patient and within a limited timeframe, enabled us to make a direct comparison between these procedures and to obtain clear clinical indications.

Second, as none of the studies reported true-negative results, we could not provide a reliable evaluation of the specificity of the imaging procedures. Third, the lack of histological confirmation of suspected distant metastatic lesions detected by PET/CT modalities was an important limitation of all the studies included in this analysis. In the absence of histological validation, we cannot exclude the possibility that some of the lesions detected by PET tracers may have been false-positive findings. Nevertheless, given the high number of patients affected by advanced disease, the likelihood of false-positive findings was relatively low. Moreover, ethical and practical reasons prevented biopsy evaluation of each lesion. Finally, among the studies included, statistically significant heterogeneity was found with regard to the pooled sensitivity of ^{18}F-DOPA PET/CT. Conversely, we did not find a significant publication bias in our analysis. This heterogeneity could be explained by differences in patient characteristics. Indeed, on exploring this aspect, we found that, after correcting the data for timing, sample size and prevalence of intestinal NETs, heterogeneity was no longer significant in most results.

5 | CONCLUSION

The present data show that both ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT are accurate diagnostic procedures in patients with intestinal NETs, yielding similar results in terms of sensitivity. However, in terms of lesion detection, we observed a non-negligible difference in favour of ^{18}F-DOPA PET/CT, with a clear trend towards significance. Thus, the use of ^{18}F-DOPA PET/CT as a first-line molecular procedure could be considered in intestinal NETs. We would advocate large, multi-centre, randomized, prospective, cost-effectiveness studies.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

A. Piccardo contributed to the conception of the study, acquired and analysed the data, and drafted the manuscript. F. Fiz contributed to the conception of the study, analysed the data and drafted the manuscript. G. Bottoni contributed to the acquisition and analysis of data. M. Ugolini contributed to the acquisition and analysis of data. W. Noordzij contributed to design of the study, analysed the data and revised the manuscript. P. Trimboli revised the manuscript critically for important intellectual content.

DATA AVAILABILITY STATEMENT

Data used to generate the present manuscript are available from the corresponding author on a reasonable request.

ORCID

Arnoldo Piccardo https://orcid.org/0000-0002-6779-1471
Francesco Fiz https://orcid.org/0000-0003-3932-1330

REFERENCES

1. Wang R, Zheng-Pywell R, Chen HA, Bibb JA, Chen H, Rose JB. Management of gastrointestinal neuroendocrine tumors. *Clin Med Insights Endocrinol Diabetes*. 2019;12:1179551419884058.
2. Scarpa A. The landscape of molecular alterations in pancreatic and small intestinal neuroendocrine tumours. *Ann Endocrinol (Paris)*. 2019;80(3):153-158.
3. Lamberti G, Brighi N, Maggio I, et al. The role of mTOR in neuroendocrine tumors: future cornerstone of a winning strategy? *Int J Mol Sci*. 2018;19(3):747.
4. Wild D, Schmitt JS, Ginj M, et al. DOTA-NOC, a high-affinity ligand of somatostatin receptor subtypes 2, 3 and 5 for labelling with various radiometals. *Eur J Nucl Med Mol Imaging*. 2003;30(10):1338-1347.
5. Campana D, Ambrosini V, Pezzilli R, et al. Standardized uptake values of (68)Ga-DOTANOC PET: a promising prognostic tool in neuroendocrine tumors. *J Nucl Med*. 2010;51(3):353-359.
6. Balogova S, Talbot JN, Nataf V, et al. 18F-fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. *Eur J Nucl Med Mol Imaging*. 2013;40(6):943-966.
7. Addeo P, Bertin JB, Imperiale A, et al. Outcomes of simultaneous resection of small bowel neuroendocrine tumors with synchronous liver metastases. *World J Surg*. 2020;44(7):2377-2384.
8. Gangi A, Manguso N, Gong J, et al. Midgut neuroendocrine tumors with liver-only metastases: benefit of primary tumor resection. *Ann Surg Oncol*. 2020;27(11):4525-4532.
9. Bozkurt MF, Virgolini I, Balogova S, et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with (68)Ga-DOTA-conjugated somatostatin receptor targeting peptides and (18)F-DOPA. *Eur J Nucl Med Mol Imaging*. 2017;44(9):1588-1601.
10. Addeo P, Poncet G, Goichot B, et al. The added diagnostic value of (18)F-fluorodihydroxyphenylalanine PET/CT in the preoperative work-up of small bowel neuroendocrine tumors. *J Gastrointest Surg*. 2018;22(4):722-730.
11. Deleval N, Pesque L, Dieudonne A, et al. Prognostic impact of bone metastases detected by (18)F-DOPA PET in patients with metastatic midgut neuroendocrine tumors. *Eur Radiol*. 2020;31(6):4166-4174.
12. de Hosson LD, van der Loo–van der Schaaf AM, Boellaard R, et al. Interlesional heterogeneity of metastatic neuroendocrine tumors based on 18F-DOPA PET/CT. *Clin Nucl Med*. 2019;44(8):612-619.
13. Imperiale A, Meuter L, Pacak K, Taieb D. Imaging of small intestine neuroendocrine neoplasms: is SSTR PET the holy grail? *J Nucl Med*. 2021;26:jnumed.121.262140.
14. McInnes MDF, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of

diagnostic test accuracy studies: the PRISMA-DTA statement. *JAMA*. 2018;319(4):388-396.
15. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536.
16. Sadeghi R, Treglia G. Systematic reviews and meta-analyses of diagnostic studies: a practical guideline. *Clin Transl Imaging*. 2017;5(2):83-87.
17. Ambrosini V, Tomassetti P, Castellucci P, 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*. 2008;35(8):1431-1438.
18. Haug A, Auernhammer CJ, Wangler B, 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*. 2009;36(5):765-770.
19. Putzer D, Gabriel M, Kendler D, 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*. 2010;54(1):68-75.
20. Ouvrard E, Chevalier E, Addeo P, et al. Intraindividual comparison of (18) F-FDOPA and (68) Ga-DOTATOC PET/CT detection rate for metastatic assessment in patients with ileal neuroendocrine tumours. *Clin Endocrinol (Oxf)*. 2021;94(1):66-73.
21. Veenstra EB, de Groot DJA, Brouwers AH, Walenkamp AME, Noordzij W. Comparison of 18F-DOPA versus 68Ga-DOTATOC as preferred PET imaging tracer in well-differentiated neuroendocrine neoplasms. *Clin Nucl Med*. 2021;46(3):195-200.
22. Ansquer C, Touchefeu Y, Faivre-Chauvet A, et al. Head-to-head comparison of 18F-DOPA PET/CT and 68Ga-DOTANOC PET/CT in patients with midgut neuroendocrine tumors. *Clin Nucl Med*. 2021;46(3):181-186.
23. Albertelli M, Dotto A, Di Dato C, et al. PRRT: identikit of the perfect patient. *Rev Endocr Metab Disord*. 2020.
24. Rufini V, Treglia G, Montravers F, Giordano A. Diagnostic accuracy of [18F]DOPA PET and PET/CT in patients with neuroendocrine tumors: a meta-analysis. *Clin Transl Imaging*. 2013;1(2):111-122.

How to cite this article: Piccardo A, Fiz F, Bottoni G, Ugolini M, Noordzij W, Trimboli P. Head-to-head comparison between ^{18}F-DOPA PET/CT and ^{68}Ga-DOTA-peptide PET/CT in detecting intestinal neuroendocrine tumours: A systematic review and meta-analysis. *Clin Endocrinol*. 2021;00:1–10. https://doi.org/10.1111/cen.14527