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Use of [^{18}F]AlF-NOTA-Octreotide PET/CT as a diagnostic test for the detection of neuroendocrine tumours: a histopathology-referenced diagnostic accuracy study

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Abstract

Background: Gallium-68-labeled somatostatin receptor positron emission tomography/computed tomography (PET/CT) is widely used for neuroendocrine tumour (NET) imaging, but implementation can be constrained by generator-dependent production and logistics. Fluorine-18 (^{18}F) tracers may facilitate centralised production and broader access. We evaluated the diagnostic performance of [^{18}F]AlF-NOTA-Octreotide (^{18}F-OC) PET/CT for NET detection using histopathology as the reference standard.

Methods: In this cross-sectional diagnostic accuracy study, patients with suspected NET who underwent ^{18}F-OC PET/CT and had histopathological confirmation were included. PET/CT positivity was defined a priori as standardised uptake value ≥8.3. We estimated sensitivity, specificity, predictive values, accuracy, likelihood ratios and 95% confidence intervals.

Results: Fifty-five patients were included (mean age 53.6 ± 15.1 years; 58.2% female). NET was confirmed in 39/55 (70.9%). PET/CT showed 92.3% sensitivity (36/39; 95% CI: 79.7–97.3) and 87.5% specificity (14/16; 95% CI: 64.0–96.5), with 94.7% positive predictive value, 82.4% negative predictive value and 90.9% accuracy. The positive likelihood ratio was 7.38, and the negative likelihood ratio was 0.09. False-negative cases were associated with small lesion size and/or biologically aggressive disease; false-positive cases showed mild uptake and were inflammatory on histopathology.

Conclusion: ^{18}F-OC PET/CT demonstrated high diagnostic performance for NET detection in a histopathology-referenced cohort. Given the logistical advantages of ^{18}F production and distribution, this tracer may support broader access to somatostatin receptor PET imaging in settings where ^{68}Ga-based tracers are constrained.

Keywords: *neuroendocrine tumours, receptors, somatostatin, positron-emission tomography and computed tomography, fluorine-18*

Clinical Study

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Introduction

Neuroendocrine tumours (NETs) are heterogeneous neoplasms arising from the diffuse endocrine system, most frequently in the gastrointestinal tract and lungs [1]. Reported incidence has increased over time, likely reflecting improved detection and heightened clinical recognition [1]. Because NETs may follow indolent courses and present with non-specific symptoms, a substantial fraction are diagnosed at advanced stages [2].

Somatostatin receptor (SSTR) imaging is central for NET localisation, staging and therapeutic decision-making [3]. While 99mTc-octreotide single-photon emission computed tomography/computed tomography (CT) was historically utilised, gallium-68-labeled somatostatin analogs now represent the gold standard due to superior sensitivity (93%–96%) and spatial resolution [4, 5]. Although [^{68}Ga]-DOTA-SSA positron emission tomography (PET)/CT is widely used for SSTR imaging, access can be limited by generator-based production, regulatory constraints and costs, especially in resource-constrained environments [6, 7]. Fluorine-18 (^{18}F) offers a longer half-life and supports centralised cyclotron production and distribution [8], potentially improving scalability.

[^{18}F]AlF-NOTA-Octreotide (^{18}F-OC) is an SSTR-targeting radiotracer with high affinity for SSTR2 and favourable biodistribution in preliminary clinical experiences [9, 10]. However, diagnostic accuracy studies anchored to histopathology remain limited. The diagnostic utility of maximum standardised uptake value (SUVmax) in ^{18}F-OC PET/CT for NETs has been explored in recent studies. An SUVmax threshold of 8.3 has been identified as optimal for distinguishing NET lesions from non-NET ones, offering the best sensitivity–specificity balance. In the most relevant study, this cutoff yielded a sensitivity of 96.3% and a specificity of 77.8%, outperforming conventional computed tomography (CT) and magnetic resonance imaging (MRI) in the same cohort [11]. While NETs typically exhibit higher SUVmax values than benign or inflammatory lesions, overlap exists. Moreover, ^{18}F-OC uptake tends to correlate with histologic grade and is generally higher in well-differentiated NETs (G1 and G2) [12]. We therefore aimed to evaluate the diagnostic performance of ^{18}F-OC PET/CT for NET detection using histopathology as the reference standard, and to contextualise its performance within the published SSTR-PET literature.

Methods

Study design and participants

This was a retrospective cross-sectional diagnostic accuracy study of consecutive patients with suspected NET evaluated between April 2021 and February 2022 at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (Mexico City, Mexico). During the study period, 18F-OC PET/CT was in the early stages of implementation at our institution as part of clinical diagnostic practice for patients with suspected or known NETs; it was not implemented solely for the purposes of this study. Patients were included if they underwent ^{18}F-OC PET/CT and had histopathological confirmation (resection or biopsy). Patients without histopathology were excluded. The study was not registered, and the full protocol is not publicly available. We report the study following STARD 2015 recommendations for diagnostic accuracy reporting (Supplementary Table 1).

PET/CT imaging protocol

Whole-body PET/CT was performed 60 minutes after intravenous administration of **260 MBq** of ^{18}F-OC using a GE Discovery PET/CT 710 scanner. Low-dose CT (120 kV, 30 mAs) was acquired for attenuation correction, followed by PET acquisition (2 minutes per bed position). Images were reconstructed using ordered-subset expectation maximisation (four iterations, eight subsets). Two nuclear medicine physicians interpreted scans blinded to histopathology results.

^{18}F-OC was produced at the Unidad Radiofarmacia-Ciclotrón (URC), Facultad de Medicina, UNAM, in a Trasis All-in-One synthesizer (Trasis, Ans, Belgium) under Good Manufacturing Practices (GMP) guidelines [13].

Reference standard and index test definition

Histopathology was used as the reference standard for NET confirmation and was performed as part of routine clinical care. Because of the retrospective design, it was not systematically recorded whether pathologists had access to PET/CT results, nor was the interval between PET/CT and histopathological confirmation consistently documented. PET/CT positivity was defined a priori as focal uptake consistent with disease with SUVmax ≥8.3, based on published work identifying this threshold as an optimal sensitivity–specificity balance for ^{18}F-labeled octreotide analog imaging [11]. Disease extent was categorised as localised or disseminated. No adverse events related to 18F-OC PET/CT were recorded, and no indeterminate PET/CT or histopathology results were included in the final diagnostic accuracy analysis.

Statistical analysis

We computed sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and likelihood ratios with 95% confidence intervals. Because pretest probability varies substantially by clinical context (e.g., general population versus referral for suspected NET), post-test probability was explored using scenario-based Bayesian updating across plausible clinical pretest probabilities (see Results). Analyses were performed using MedCalc v20.0 (MedCalc Software Ltd).

Ethics

The protocol was approved by the institutional ethics committee (REG. CONBIOÉTICA-09-CEI-011-20160627). Written informed consent was obtained from all participants, including consent for publication of anonymised clinical and imaging data.

Results

Participant flow and baseline characteristics

Ninety-six patients were evaluated; 55 met inclusion criteria after excluding 41 without histopathological confirmation. The cohort had a mean age of 53.6 ± 15.1 years and 58.2% were female. NET was confirmed in 39/55 (70.9%). The participant inclusion process is shown in Figure 1. Among NET cases, most were well differentiated; metastatic disease was present in 29/39 (74.4%), most commonly involving liver and retroperitoneal lymph nodes. Non-NET diagnoses included Cushing's disease and paraganglioma (Table 1 and Figure 2).

Diagnostic performance

Using histopathology as the reference standard, ^{18}F-OC PET/CT identified 36 true-positive and 14 true-negative results, with 3 false-negative and 2 false-positive findings. Sensitivity was 92.3% (36/39; 95% CI: 79.7–97.3) and specificity 87.5% (14/16; 95% CI: 64.0–96.5). The PPV was 94.7%, the NPV was 82.4% and overall accuracy was 90.9%. The positive likelihood ratio (LR+) was 7.38 and the negative likelihood ratio (LR−) was 0.09 (Table 2).

False-negative and false-positive cases

False-negative findings occurred in three situations: (i) a small (5 mm) grade 1 pancreatic NET with low uptake; (ii) a grade 3 NET with high proliferative activity (Ki-67 >20%) and (iii) a gastrinoma in a patient with impaired renal function. False-positive findings were characterised by mild uptake and corresponded to inflammatory processes on histopathology.

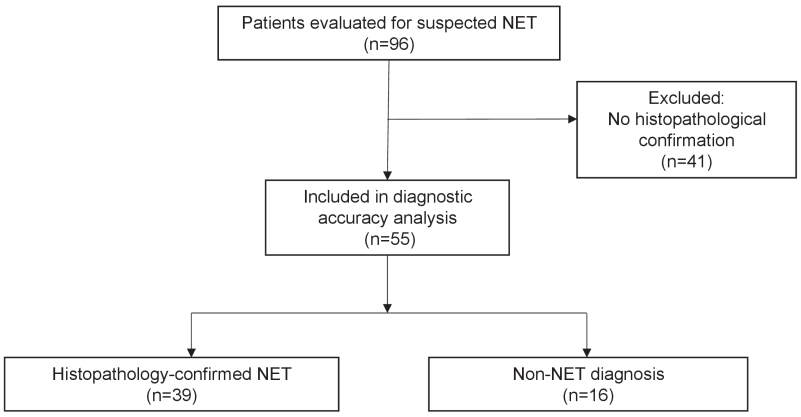

Figure 1. Participant flow diagram. Of 96 patients evaluated for suspected NET, 41 were excluded because histopathological confirmation was unavailable. The final diagnostic accuracy cohort included 55 patients, of whom 39 had histopathologically confirmed NET and 16 had non-NET diagnoses.

Table 1. Baseline characteristics and tumour features.

Characteristic	Overall (*n* = 55)	NET (*n* = 39)	Non-NET (*n* = 16)
Age, years (mean ± SD)	53.6 ± 15.1	56.8 ± 14.0	45.9 ± 15.0
Female sex, *n* (%)	32 (58.2)	19 (59.3)	13 (40.6)
NET confirmed, *n* (%)	39 (70.9)	39 (100)	0 (0)
Tumour grade (NET)			
Grade 1, *n* (%)	—	30 (76.9)	—
Grade 2, *n* (%)	—	7 (17.9)	—
Grade 3, *n* (%)	—	1 (2.6)	—
Grade missing/NR, *n* (%)	—	1 (2.6)*	—
Metastatic disease (NET), *n* (%)	—	29 (74.4)	—
Liver metastasis (NET), *n* (%)	—	23 (58.9)	—
Retroperitoneal LN metastasis (NET), *n* (%)	—	19 (48.7)	—
Secretory	—	11 (28.2)	—
Gastrin	—	4 (10.2)	—
Insulin	—	4 (10.2)	—
5-hydroxytryptamine	—	2 (5.1)	—
Glucagon	—	1 (2.5)	—
Non-NET diagnoses			
Cushing's disease, *n* (%)	—	—	8 (50.0)
Paraganglioma, *n* (%)	—	—	1 (6.3)
Others, *n* (%)	—	—	7 (43.8)

Values are *n* (%) unless otherwise indicated

*One patient had confirmed NET, but tumour grade was not reported in the available histopathology report

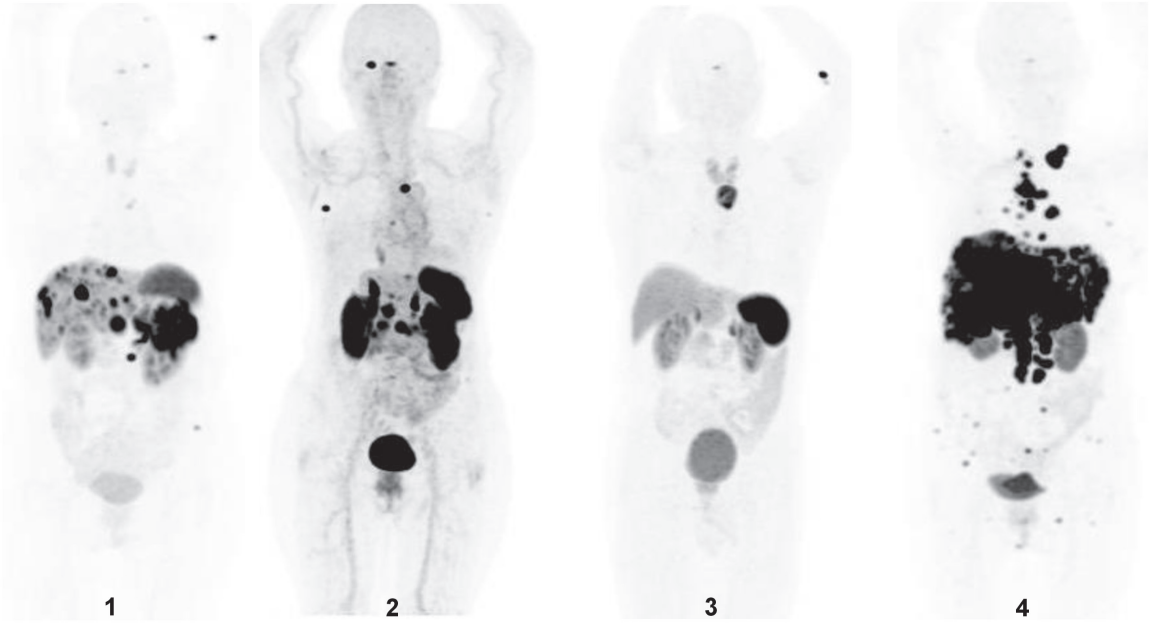

Figure 2. Representative ^{18}F-OC PET/CT scans from four patients with NETs. Maximum intensity projection (MIP) images are shown:

1. **69-year-old female with a grade 2 NET, primary lesion located in the kidney and metastatic involvement of the liver and retroperitoneal lymph nodes.**
2. **65-year-old female with a grade 1 NET located in the ileum, presenting with metastases to axillary, mediastinal and retroperitoneal lymph nodes, as well as the liver, pancreas and right orbital muscle.**
3. **63-year-old male with a localised pulmonary carcinoid tumour.**
4. **52-year-old female with a grade 1 NET of pancreatic origin, showing metastases to the liver, bone and retroperitoneum. The largest lesion measured 16.3 cm.**

Table 2. Diagnostic performance of 18F-OC PET/CT (histopathology reference).

Measure	Value	95% CI
True positives (TP)	36	—
False positives (FP)	2	—
True negatives (TN)	14	—
False negatives (FN)	3	—
Sensitivity	92.3% (36/39)	79.7–97.3
Specificity	87.5% (14/16)	64.0–96.5
PPV	94.7% (36/38)	82.7–98.5
NPV	82.4% (14/17)	59.0–93.8
Accuracy	90.9% (50/55)	80.4–96.1
LR+	7.38	2.01–27.08
LR−	0.09	0.03–0.26

Histopathology served as the reference standard. PPV/NPV are reported for this study cohort and may vary with pretest probability

Scenario-based post-test probability (Bayesian interpretation)

Given LR+ = 7.38 and LR− = 0.09, the post-test probability varies according to the clinical pretest probability (Table 3). Across plausible referral-setting scenarios, a positive PET/CT substantially increases the probability of NET (from 10% to 45.1% and from 70% to 94.5%), whereas a negative PET/CT markedly lowers it at lower-to-intermediate pretest probabilities (to 1.0%–8.3% for pretest values of 10%–50%). At higher pretest probability (70%), a negative result reduces the probability to 17.4%, underscoring that residual risk may remain when clinical suspicion is high and supporting the need for continued clinicopathologic correlation in selected cases. These scenario-based Bayesian effects are graphically represented in Figure 3.

Discussion

In this histopathology-referenced diagnostic accuracy study, ^{18}F-OC PET/CT demonstrated high sensitivity and specificity for NET detection, with LR+ and LR− values consistent with a clinically useful test in referral settings. While no within-patient head-to-head comparison against [^{68}Ga]-DOTA-SSA PET/CT was performed, the observed performance is within ranges commonly reported for SSTR-PET imaging in NET management [7]. From an implementation perspective, ^{18}F-OC PET/CT may offer practical advantages over ^{68}Ga-based tracers. The longer half-life of ^{18}F enables centralised cyclotron production and regional distribution to multiple PET centers, whereas ^{68}Ga-based imaging often depends on local generator availability and radiopharmacy infrastructure. Automated GMP-compliant production of ^{18}F-OC has been described, supporting its technical feasibility for clinical workflows [14]. These features may reduce logistical barriers in centers without access to ^{68}Ge/^{68}Ga generators; however, formal cost-effectiveness analyses comparing ^{18}F-OC with [^{68}Ga]-DOTA-SSA tracers are still needed, particularly in lower-resource settings.

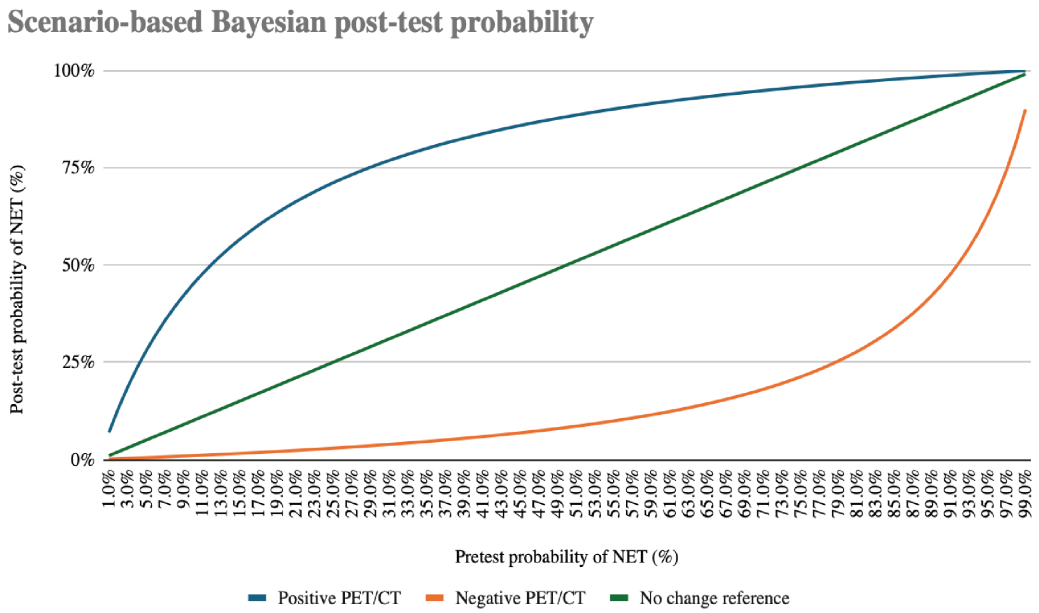

Figure 3. Scenario-based Bayesian post-test probability curves for ^{18}F-OC PET/CT. Post-test probabilities after positive and negative PET/CT results are shown across a continuous range of clinically plausible pretest probabilities using LR+ = 7.38 and LR− = 0.09. The positive PET/CT curve illustrates the increase in post-test probability after a positive result, whereas the negative PET/CT curve illustrates the reduction in post-test probability after a negative result.

Table 3. Scenario-based post-test probability (Bayesian interpretation). (LR+ = 7.38; LR− = 0.09).

Pretest probability	Post-test if PET/CT positive	Post-test if PET/CT negative
10%	45.10%	1%
30%	76%	3.70%
50%	88.10%	8.30%
70%	94.50%	17.40%

Post-test probabilities were calculated using Bayes' theorem with odds: pretest odds = p/(1−p); post-test odds = pretest odds × LR; post-test probability = odds/(1+odds)

False-negative cases highlight known challenges for SSTR-targeted imaging: very small lesions, dedifferentiated or high-grade tumours with reduced SSTR expression and physiologic or patient-related factors that may alter biodistribution. In such scenarios, complementary imaging and clinicopathologic correlation remain essential [15–17]. It is also worth noting that the lower positron energy of 18F compared with 68 Ga (0.63 versus 1.9 MeV) may improve PET image quality and spatial resolution, potentially providing an advantage for the evaluation of small lesions.

False positives underscore that mild uptake can occur in inflammatory conditions and in physiologic sites of higher SSTR expression; standardised interpretation criteria and awareness of pitfalls (e.g., pancreatic uncinate uptake, splenosis and inflammatory disease) are necessary [17–19].

At our institution, ^{18}F-OC PET/CT was incorporated into the diagnostic workflow for NET evaluation, in line with related investigations from other countries and supported by the local availability of cyclotron-based ^{18}F production. Chen *et al* [11] reported that ^{18}F-OC PET/CT improved detection and evaluation of neuroendocrine neoplasms compared with contrast-enhanced CT/MRI. Hou *et al* [12] characterised biodistribution and tumour uptake of ^{18}F-OC in neuroendocrine neoplasms. In addition, Pauwels *et al* [20] reported superior lesion detection with ^{18}F-OC compared with [^{68}Ga]-DOTA-TATE/NOC in a prospective multicenter study. The major provider of PET radiopharmaceuticals in Mexico City is the URC-UNAM, which introduced ^{68}Ga-based radiopharmaceuticals in 2013. However, the high demand for these radiopharmaceuticals, the limited activity and elevated cost of ^{68}Ge/^{68}Ga generators, and the relatively short half-life of ^{68}Ga (68 minutes) prompted the shift to ^{18}F. Additionally, the country's current installed base of 12 cyclotron facilities and approximately 70 PET tomographs [21] supports and promotes the widespread use of ^{18}F-based radiopharmaceuticals.

Limitations include the single-center design, modest sample size and potential selection bias introduced by excluding patients without histopathology. Additionally, without a simultaneous comparator arm ([^{68}Ga]-DOTA-SSA), direct comparative claims cannot be made. Although Mexico has an expanding PET infrastructure, access remains concentrated in selected urban and tertiary-care centers. Therefore, PET-based diagnosis may remain restricted regardless of the radiotracer used.

Although current guidelines support SSTR-PET imaging for NET management [17, 22], ^{18}F-OC is not yet widely incorporated as a standard tracer. Therefore, our findings should be considered supportive evidence for further validation and future multicenter, head-to-head and health-economic studies are needed to define its role in clinical guidelines.

Conclusion

^{18}F-OC PET/CT showed high diagnostic accuracy for NET detection when referenced to histopathology. Its ^{18}F-based production logistics may support broader access to SSTR PET imaging, particularly in settings where ^{68}Ga-based tracers are constrained.

List of abbreviations

CI, confidence interval; LR, likelihood ratio; NET, neuroendocrine tumour; NPV, negative predictive value; PET/CT, positron emission tomography/computed tomography; PPV, positive predictive value; SSTR, somatostatin receptor; SUVmax, maximum standardised uptake value.

Acknowledgments

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Author contributions

PBCM: Conceptualisation, methodology, data curation, writing (original draft). RFM: Writing (review and editing), manuscript revision, critical feedback. EIÁ: Resources, validation, visualisation. MAÁR: Supervision, project administration, radiopharmaceutical synthesis. AARA: Formal analysis, investigation, writing (review and editing).

Data availability

Data are not publicly available due to privacy and ethical restrictions, but may be available from the corresponding author upon reasonable request.

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Supplementary Table

Supplementary Table 1. Completed STARD 2015 checklist with page and section references.

Section/topic	No.	STARD 2015 checklist item	Location in manuscript
Title or abstract			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values or AUC).	p. 1, Title page; p. 3, Abstract.
Abstract			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts).	p. 3, Abstract.
Introduction			
	3	Scientific and clinical background, including the intended use and clinical role of the index test.	pp. 5-6, Introduction.
	4	Study objectives and hypotheses.	p. 6, Introduction, final paragraph.
Methods			
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study).	p. 6, Methods, Study design and participants.
Participants	6	Eligibility criteria.	p. 6, Methods, Study design and participants.
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry).	p. 6, Methods, Study design and participants.
	8	Where and when potentially eligible participants were identified (setting, location and dates).	p. 6, Methods, Study design and participants.
	9	Whether participants formed a consecutive, random or convenience series.	p. 6, Methods, Study design and participants.
Test methods	10a	Index test, in sufficient detail to allow replication.	pp. 6-7, Methods, PET/CT imaging protocol.
	10b	Reference standard, in sufficient detail to allow replication.	pp. 6-7, Methods, Study design and participants; Reference standard and index test definition.
	11	Rationale for choosing the reference standard (if alternatives exist).	p. 7, Methods, Reference standard and index test definition. Histopathology is specified as the reference standard for NET confirmation.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory.	p. 7, Methods, Reference standard and index test definition.
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory.	pp. 6-7, Methods, Study design and participants; Reference standard and index test definition. Histopathology classified cases as NET or non-NET.
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test.	p. 6, Methods, PET/CT imaging protocol. Readers were blinded to histopathology results.
	13b	Whether clinical information and index test results were available to the assessors of the reference standard.	p. 7, The evaluators of the reference standard did not have access to clinical information and index test results.

Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy.	p. 7, Methods, Statistical analysis; pp. 23-24, Tables 2-3.
	15	How indeterminate index test or reference standard results were handled.	p. 7, No indeterminate PET/CT or histopathology results were included in the final diagnostic accuracy analysis.
	16	How missing data on the index test and reference standard were handled.	p. 6, Methods, Study design and participants; p. 8, Results, Participant flow. Patients without histopathological confirmation were excluded.
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory.	Not applicable; no subgroup or variability analysis was performed.
	18	Intended sample size and how it was determined.	p. 6, The cohort corresponds to consecutive patients with available PET/CT and histopathology during the study period.
Results			
Participants	19	Flow of participants, using a diagram.	p. 8, Results, Participant flow and baseline characteristics; p. 25, Figure 1.
	20	Baseline demographic and clinical characteristics of participants.	p. 8, Results, Participant flow and baseline characteristics; p. 22, Table 1.
	21a	Distribution of severity of disease in those with the target condition.	p. 8, Results; p. 22, Table 1. Tumour grade, metastatic disease, liver metastasis, and retroperitoneal lymph node metastasis are reported for NET cases.
	21b	Distribution of alternative diagnoses in those without the target condition.	p. 8, Results; p. 22, Table 1. Non-NET diagnoses are reported.
	22	Time interval and any clinical interventions between index test and reference standard.	p. 7, The time interval between PET/CT and histopathological confirmation varied according to clinical workflow.
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard.	p. 8, Results, Diagnostic performance; p. 23, Table 2.
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals).	p. 8, Results, Diagnostic performance; p. 23, Table 2.
	25	Any adverse events from performing the index test or the reference standard.	p. 7, No adverse events related to 18F-OC PET/CT were recorded.
Discussion			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability.	p. 11, Discussion, Limitations paragraph.
	27	Implications for practice, including the intended use and clinical role of the index test.	pp. 9-11, Discussion; p. 11, Conclusions.
Other information			
	28	Registration number and name of registry.	p. 6, The study was not registered.
	29	Where the full study protocol can be accessed.	p. 6, The full protocol is not publicly available.
	30	Sources of funding and other support; role of funders.	p. 15, Funding; p. 14, Acknowledgments; p. 13, Conflicts of interest.

Source: STARD 2015 checklist for diagnostic accuracy studies. Adapted from Bossuyt et al. STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies

Note: Page numbers refer to the revised manuscript draft rendered from the submitted Word file. They should be verified after any final formatting or pagination changes