Comparison of gallium-68 somatostatin receptor and ^{18}F-fluorodeoxyglucose positron emission tomography in the diagnosis of neuroendocrine tumours: A systematic review and meta-analysis

Xue Liu[1] MD,
Ning Li[2] MD,
Tao Jiang[1] MD,
Huaiwei Xu[1] MD,
Qilian Ran[3] MD,
Zhen Shu[1] MD,
Jiang Wu[1] MD,
Youcheng Li[1] MD,
Shiliang Zhou[1] MD,
Bao Zhang[1] MD

1. Department of Nuclear Medicine, The First Pepole's Hospital of Huaihua City, 418000, Hunan, People's Republic of China
2. Department of Pathology, The First Pepole's Hospital of Huaihua City, 418000, Hunan, People's Republic of China
3. Department of Nursing, The First Affiliated Hospital of Hunan University of Medicine, 418000, Hunan, People's Republic of China

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Corresponding authors:
Xue Liu MD,
Department of Nuclear Medicine, The First Pepole's Hospital of Huaihua City,
No.144 Jinxi Road, Hecheng District, Hunan, 418000,
People's Republic of China
thyroid@126.com

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Abstract

Objective: A meta-analysis was performed to compare the diagnostic performance of gallium-68 (^{68}Ga) somatostatin receptor positron emission tomography (^{68}Ga-SSTR PET) and fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET in patients with neuroendocrine tumours (NET) and whether the two imaging modalities can be mutually substituted in clinical work. **Methods:** We performed electronic literature searches of the MEDLINE, PubMed, Embase and Cochrane Library databases for English-language articles from the earliest available date of indexing through 30 July 2019. We calculated the pooled sensitivity, specificity and diagnostic odds ratios (DOR) with 95% confidence intervals (95% CI) of ^{68}Ga-SSTR PET and ^{18}F-FDG PET in NET. We drew a summary receiver operator characteristic (SROC) curve and calculated the area under the curve (AUC) to measure the accuracy of ^{68}Ga-SSTR PET and ^{18}F-FDG PET in patients or lesions with NET. **Results:** Thirty studies comprising 3401 patients and 5793 lesions with NET were included in this meta-analysis. The pooled sensitivity, sensitivity, DOR and AUC for ^{68}Ga-SSTR PET or PET/computed tomography (CT) in the diagnosis of NET, based on lesion patient, were 0.92(0.89-0.95), 0.91(0.83-0.95),119(51-282) and 0.96(0.94-0.98), and based on lesion, were 0.95(0.86-0.98), 0.93(0.83-0.97), 229(43-1205) and 0.98(0.96-0.99), respectively. The pooled sensitivity, sensitivity, DOR and AUC for ^{18}F-FDG PET or PET/CT in NET were 0.70(0.41-0.89), 0.97(0.70-1.00), 67(7-612) and 0.94(0.92-0.96), respectively, when analyzed on a per-patient basis. The pooled sensitivities of ^{68}Ga-SSTR PET/CT were 0.923 (95% CI: 0.884-0.952), 0.902 (0.862-0.934) and 0.578 (0.482-0.669) in the G1(ki67,≤2%), G2(ki67,>3%,≤20%) and G3(ki67, >20%) groups based on patients with NET, respectively. The pooled sensitivities of ^{18}F-FDG PET/CT were 0.378 (0.319-0.440), 0.554 (0.492-0.615) and 0.712 (0.633-0.783) in the G1, G2 and G3 groups based on patients with NET, respectively. **Conclusions:** The ^{68}Ga-SSTR PET has highly sensitive and had a greater diagnostic value than ^{18}F-FDG PET for patients with NET. Fluorine-18-FDG PET, however, had significant specificity than ^{68}Ga-SSTR PET. The ^{68}Ga-SSTR has high sensitivity in G1/G2 NET, while ^{18}F-FDG has a low positive rate. In G3 NET, however, the opposite is true. Therefore, the ^{68}Ga-SSTR PET and ^{18}F-FDG PET modalities are complementary rather than substitutive in clinical practice.

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Introduction

Neuroendocrine tumours (NET) are defined as a class of slow-growing tumours that are mainly distributed in the lungs, gastrointestinal tract or pancreas [1]. The 2010 European Neuroendocrine Tumor Society (ENETS)/World Health Organization (WHO) classification separates NET according to the mitotic index into low-grade (G1,ki67,≤2%), moderate-grade (G2, ki67, 3-20%), high-grade (G3, ki67, >20%) [2]. Neuroendocrine tumours are typically considered rare tumours, but each year, an estimated 8,000 individuals are newly diagnosed from Surveillance, Epidemiology and End Results reports, and the annual incidence has increased fivefold since 1973 [3]. This change has been attributed, in a way, to improved diagnostic techniques focused on the disease. Despite the correct staging and grading of the tumour, the overall 5-year survival rate is only approximately 75% [1]. The clinical manifestations and outcomes of and therapies for NET mainly depend on the organ of origin, hormonal excretions, and tumour grade and stage, for which the overwhelming majority of imaging systems offer inestimable diagnostic information [4].

Hence, accurate early diagnosis and detection of metastases are essential for prognosis and treatment choices in all malignancies. Traditional imaging techniques, such as computed tomography (CT), ultrasonography (US), and magnetic resonance imaging (MRI), have been used to distinguish benign and malignant NET; however, their results

are limited because of the small sizes, variable anatomic locations and low metabolic rates of the NET [5, 6]. Indium-111 (^{111}In) octreotide scanning is a class of functional imaging that can be applied to detect NET because the majority of NET forcefully secrete subtype 2 of the somatostatin receptor (SSTR-2), and octreotide is an integrated analogue of somatostatin with a known affinity to SSTR-2 [4]. Although an octreotide scan with single photon emission computed tomography (SPECT) has been used in the medical domain for nearly 30 years and is considered the gold standard for the detection of NET, the technique has several limitations, including poor image quality, the low resolution of γ-ray scintigraphy, a spatial resolution of approximately 1cm and prolonged imaging protocols [7, 8].

Consequently, to overcome the deficiencies and disadvantages of ^{111}In octreotide scans, newer, higher-affinity somatostatin analogues have been produced, including 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic-acid-D-Phe1-Tyr3-octreotide (DOTA-TOC), DOTA-d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr (DOTA-TATE), and DOTA-[Nal3]-octreotide (DOTA-NOC). Gallium-68 (^{68}Ga) can co-label with these DOTA-based substances to form promising SSTR (^{68}Ga-SSTR) scintigraphy imaging agents that can act as position emitter mixtures in positron emission tomography (PET) to provide better image quality and spatial resolution than ^{111}In-SPECT. Positron emission tomography is a functional imaging modality that has incredibly fine spatial resolution and high metabolic imaging, and ^{68}Ga-SSTR has been shown to rapidly localize to NET lesions [9]. Several previous studies [10-12] have suggested the value of ^{68}Ga-SSTR PET or PET/CT in detecting and functionally characterizing NET. However, hardly any of the studies have well controlled clinical trials, the gold standards in the majority of these studies are not optimal, and no papers with strict quality control have been published. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET, a non-invasive functional imaging modality, has been proposed as an alternative to tissue sampling for the determination of the aggressiveness of tumours and has shown prognostic value in several kinds of cancer other than NET [13].

Several papers have reported the diagnostic accuracy of ^{68}Ga-SSTR PET or PET/CT for the characterization of NET, evaluating a wide range of sensitivities and specificities [9, 14, 15]. Although several meta-analysis articles have confirmed the high diagnostic accuracy of ^{68}Ga-SSTR PET or PET/CT in NET, there has been no meta-analysis to perform the comparison of ^{68}Ga-SSTR or ^{18}F-FDG PET/CT divides into the three categories according to histology.

The aim of this systematic review and meta-analysis of published data is to compare the application value of ^{68}Ga-SSTR and ^{18}F-FDG PET or PET/CT in characterizing NET and whether they can be mutually substituted to provide more evidence-based data and useful information for clinicians.

Methods

Data sources and search strategy

We performed electronic literature searches of the MEDLINE, PubMed, Embase and Cochrane Library databases for English-language articles from the earliest available date of indexing through 31 December 2019. We also hand-searched the reference lists of the identified publications for additional studies.

The following terms were used for the selection of studies: (1) "PET" OR "positron emission tomography" OR "positron emission tomography/computed tomography" OR "PET/CT" "positron emission tomography-computed tomography" OR "PET/CT"; (2) ("neurosecretory" OR "neurosecretory systems" OR "neuroendocrine") AND ("neoplasm " OR "neoplasms" OR "cancer" OR "tumour" OR "carcinoma"; (3) "Gallium-68" OR "Ga-68" OR "68-Gallium" OR "68-Ga"; (4) "fluorodeoxyglucose f18" OR ("fluorodeoxyglucose" AND "F18") OR "fluorodeoxyglucose F18" OR ("18F" AND "FDG") OR "18F FDG".

Study selection

The inclusion criteria for the relevant studies were as follows: (a) ^{68}Ga-SSTR PET or PET/CT was used to identify and characterize NET; (b) subjects were identified as having NET by histopathological or imaging examinations or clinical follow-up; (c) either sufficient data to calculate sensitivity and specificity of PET or PET/CT in NET or absolute numbers of true-positives (TP), true-negatives (TN), false-positives (FP), and false-negatives (FN) were reported; and (d) analyses were performed on a per-patient or per-lesion basis.

The exclusion criteria were as follows: (a) review articles, animal experiments, editorials or letters, comments and conference proceedings; (b) overlapping papers; (c) insufficient data to reassess sensitivity and specificity from individual studies; (d) lack of access to full text; (e) a sample size of fewer than 10 patients or lesions with NET.

Data extraction

A data abstraction sheet was developed. Two reviewers independently assessed the collected data and included basic information (authors, year of publication, and country of origin), the study design (prospective or retrospective), patient characteristics (gender, age), diagnostic criteria for determining NET, whether the blinding protocols were described (yes or no), imaging agent (^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC or ^{18}F-FDG), sample size (patient or lesion), imaging modality (PET or PET/CT), and agent dosage. Each study was analyzed to retrieve the number of TP, TN, FP, and FN findings on PET or PET/CT in detecting NET, according to the reference standard. Only studies providing such complete information were finally included in the meta-analysis.

Quality assessment

The methodological quality of the included studies was critically appraised based on the 15 items of the modified Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) [16, 17] as recommended by the Cochrane Collaboration. Each item was evaluated with "High", "Low" or "Unclear".

Statistical analysis and data synthesis

All data from each eligible study were extracted. Descriptive statistics such as the mean and standard deviation were used to summarize continuous variables, while count and percentage were used for categorical variables. The primary objective was to estimate the sensitivity, specificity, positive likelihood ratios, negative likelihood ratios and diagnostic odds ratios (DOR) with 95% confidence intervals (95% CI). A DOR can be calculated as the ratio of the odds of positivity in a disease state relative to the odds of positivity in the non-disease state, with higher values indicating better discriminatory test performance [18]. A bivariate normal random-effects model for measures was used to analyse and pool the diagnostic performance of ^{68}Ga-SSTR PET or PET/CT in the established literature [19]. This method accounts for variation occurring between studies as well as the correlation between sensitivity and specificity. Each data point of the summary receiver operator characteristic (SROC) graph comes from an individual study; then, an SROC curve is formed based on these points to generate a smooth curve to reveal the pooled accuracy [20]. The area under the curve (AUC) of SROC was calculated to measure the accuracy of ^{68}Ga-SSTR PET and ^{18}F-FDG PET in diagnosing patients or lesions with NET. The I-square statistic was calculated and the Cochrane Q test was performed to test for statistical heterogeneity between the studies on the basis of the random-effects analysis [21]. Publication bias was examined using an effective sample size funnel plot and the associated regression test of asymmetry described by Deeks and colleagues [22]. When statistical heterogeneity was substantial, we performed subgroup analysis or meta-regression to identify potential sources of bias [23]. Tests for significance were two-tailed, with a statistically significant P-value threshold of 0.05. Statistical analyses were carried out using commercial software programs (STATA, version 12.0; StataCorp LP).

Results

Literature search and study selection

After the comprehensive, computerized search was performed and references lists were extensively cross-checked, our research yielded 1965 records. Reviewing titles and abstracts, 1575 records were excluded because they were non-human studies, duplicated reports, reviews, editorials, conference abstracts or small case series. Additionally, 370 uncorrelated abstracts were removed. In total, 74 articles remained. By reading the full texts, 44 articles were eliminated because of a lack of sufficient information to calculate sensitivity and specificity. Finally, 30 studies met all inclusion (and none of the exclusion) criteria and were included in this systematic review and meta-analysis. No other articles were found after screening the references of these articles. The detailed procedure implemented for article selection in the meta-analysis is presented in Figure 1.

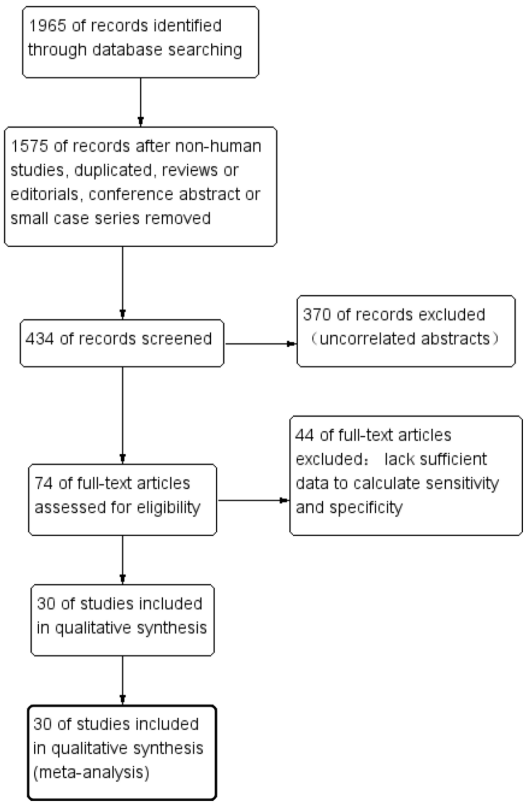

Figure 1. Summary of the study selection process. After the comprehensive, our research yielded 1965 records. Reviewing titles and abstracts, 1575 records were excluded because they were non-human studies, duplicated reports, reviews, editorials, conference abstracts or small case series. Three hundred and seventy uncorrelated abstracts were removed. In total, 74 articles remained. By reading the full texts, 44 articles were eliminated because of a lack of sufficient information to calculate sensitivity and specificity. Finally, 30 studies were included in this systematic review and meta-analysis.

Characteristics of the included studies

The major characteristics of the 30 studies included in the meta-analysis are described in Table 1. The thirty articles [10-13, 24-49] were published between 2007 and 2019, including 11 prospective studies [12, 13, 24, 26, 28, 34, 35, 37, 44, 47, 49] and 19 retrospective studies. Four studies [13, 24-26] used PET, and others used PET/CT as the imaging modality. The number of cases in each study ranged from 19 to 2475. There were a total of 3401 patients and 5793 NET lesions in the included studies, and the ages of the patients ranged from 18 to 81 years. We conducted all analyses based on per-patient and/or per-lesion data. Across all studies, twenty-one analyses were performed on a per-patient basis. Gallium-68-DOTATOC was analysed in 10 of these studies, ^{68}Ga-DOTATATE in 10, ^{68}Ga-DOTANOC in 6 and ^{18}F-FDG in 12. Nine articles performed analyses on a per-lesion-basis. Gallium-68-DOTATOC was analysed in 6 of these studies, ^{68}Ga-DOTA-NOC in 2 studies and ^{18}F-FDG in 1 study. There were 11 articles that included both patient-based and lesion-based analyses. Twelve studies[40-49] analyzed the value of ^{68}Ga-SSTR or ^{18}F-FDG in PET/CT in G1, G2,and G3 of NET (Supplementary Table 1).

Table 1. *Basic study and patient characteristics.*

First author	Publication year	Country	Patients/ Lesion(n)	Gender （M/F）	Age#	Study type	Blind	Imaging modality	Imaging agent (Activity)	Image analysis	Diagnostic criteria	(Refs.)
Gabriel	2007	Austria	84/389	48/36	58.2±12.2	P	NG	PET	^{68}Ga-DOTA-TOC(100-150MBq)	Semi-quantitative	Histology,imaging examination,Follow-up	[24]
Versari	2010	Italy	19/29	11/8	56(21-80)	R	blind	PET	^{68}Ga-DOTA-TOC(1.5-2MBq/Kg)	visual	biopsy and/or surgery	[25]
Srirajaskanthan	2010	United Kingdom	51/226	27/24	55.50 (18-80)	P	blind	PET	^{68}Ga-DOTA-TATE(120-200MBq)	visual	Histology	[26]
Ruf	2011	Germany	51/510	25/26	57±13	R	blind	PET/CT	^{68}Ga-DOTA-TOC(100-120MBq)	visual	Histology,follow-up	[27]
Naswa	2011	India	109/NG	58/51	50	P	blind	PET/CT	^{68}Ga-DOTA-NOC(132-222MBq)	Semi-quantitative and visual	Histology	[28]
Łapińska	2011	Poland	97/NG	40/57	54(18-81)	R	NG	PET/CT	^{68}Ga-DOTA-TATE(111-185MBq)	visual	Histology	[29]
Mayerhoefer	2012	Austria	55/2475	22/33	61.9±10.8	R	blind	PET/CT	^{68}Ga-DOTA-TOC(150 MBq)	Visual	Histology, imaging examinations	[30]
Haug	2012	Germany	104/NG	52/52	58±16	R	NG	PET/CT	^{68}Ga-DOTA-TATE(200 MBq)	Visual	Histology	[32]
Schraml	2013	Germany	51/593	26/25	57	P	blind	PET/CT	^{68}Ga-DOTA-TOC(150 MBq)	Visual	Histology	[34]
Venkitaraman	2014	India	32/NG	15/17	34.22±12.03	P	blind	PET/CT	^{68}Ga-DOTA-TOC(74-111MBq)	Semi-quantitative	Histology	[12]
Naswa	2014	India	51/103	30/21	48.8±38.8	R	blind	PET/CT	^{68}Ga-DOTA-NOC(132-222MBq)	Semi-quantitative and visual	Histology	[11]
Haug	2014	Germany	63/NG	34/29	58±14	R	blind	PET/CT	^{68}Ga-DOTA-TATE(200 MBq)	visual	Histology	[10]
Morgat	2016	France	19/79	7/12	47±13	P	blind	PET/CT	^{68}Ga-DOTA-TOC(1.5 MBq/kg)	visual	Histology	[35]
Ismaheel	2017	Africa	203/NG	100/103	49.31±18.70	R	NG	PET/CT	^{68}Ga-DOTA-TATE(150-250MBq)	visual	Histology	[38]

(continued)

Ambrosini	2012	Italy	131/NG	NG	NG	R	NG	PET/CT	^{68}Ga-DOTA-NOC(120-185MBq)	visual	Histology	[31]
Skoura	2015	United Kingdom	728/NG	340/388	15-86	R	NG	PET/CT	^{68}Ga-DOTA-TATE(250 MBq)	visual	Histology,imaging examinations, follow-up	[36]
Chen	2017	Taiwan, China	36/NG	19/17	24-84	P	blind	PET/CT	^{68}Ga-DOTA-TOC(2-5mCi);^{18}F-FDG(NG)	Semi-quantitative	Histology,follow-up	[37]
Niraj	2014	India	51/51	30/21	14-74	R	blind	PET/CT	^{68}Ga-DOTA-NOC(30-50mCi);^{18}F-FDG(10mCi)	Semi-quantitative	Histology,imaging examinations, follow-up	[33]
Jackson	2017	Australia	49/NG	15/34	45.2±14.3	R	NG	PET/CT	^{18}F-FDG(3.7 MBq/kg)	visual	Histology	[39]
Rinzivillo	2018	Italy	93/NG	41/52	50-68	P	NG	PET	^{18}F-FDG(2.96-3.7MBq/kg)	Semi-quantitative	Histology	[13]
Bromińska	2018	Poland	73/NG	33/40	61(39–77)	R	NG	PET/CT	^{18}F-FDG(4MBq/kg)	Semi-quantitative	Histology	[40]
zhang	2018	china	83/NG	50/33	56	R	NG	PET/CT	^{18}F-FDG(3.7 MBq/kg); ^{68}Ga-DOTA-TATE(100–200MBq)	Semi-quantitative	Histology	[41]
Cingarlini	2017	Italy	35/NG	19/16	59 (41-84)	R	NG	PET/CT	^{68}Ga-DOTATOC(1.5 MBq/kg); ^{18}F-FDG(2.96 MBq/kg)	Semi-quantitative	Histology	[42]
Nikita	2017	India	51/NG	25/26	48	R	NG	PET/CT	NG	Semi-quantitative	Histology	[43]
Wild	2013	United Kingdom	10/248	10/8	25–85	P	NG	PET/CT	^{68}Ga-DOTATATE(155 ± 17MBq); ^{68}Ga-DOTA-NOC(155±12MBq)	Semi-quantitative	Histology	[44]
Panagiotidis	2017	United Kingdom	104/NG	55/49	20–90	R	NG	PET/CT	^{18}F-FDG(370 MBq); ^{68}Ga-DOTA-TATE(120–200MBq)	Semi-quantitative	Histology	[45]
Kayani	2008	United Kingdom	48/302	25/13	53	R	NG	PET/CT	^{18}F-FDG(370 MBq); ^{68}Ga-DOTA-TATE(120–200MBq)	Semi-quantitative	Histology	[46]
Johnbeck	2016	Denmark	100/NG	60/40	35-87	P	NG	PET/CT	^{18}F-FDG(4 MBq/kg)	Semi-quantitative	Histology	[47]
Nilica	2016	Austria	66/NG	38/28	57.2±7.0	R	NG	PET/CT	^{18}F-FDG(200-300 MBq); ^{68}Ga-DOTATOC(100-150MBq)	Semi-quantitative	Histology	[48]
Majala	2019	Finland	31/NG	20/11	60±18	P	NG	PET/CT	^{18}F-FDG(321.9 ± 67.3MBq); 68Ga-DOTANOC(143.8 ± 17.1MBq)	Semi-quantitative	Histology	[49]

#Age(Mean/median/range) ;NG,not given; P, prospective； R, retrospective; M, man; F, female; PET/CT,Positron emission tomography/ Computed tomography.

Quality assessment and publication bias

The risk of bias and applicability summary are shown in Figures 2 and 3, respectively, and the quality of the suitable articles was indicated to be adequate. To evaluate potential publication bias, a test was carried out with Deeks's funnel plots. The number of times that ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC and ^{18}F-FDG examination methods were performed on a per-patient or per-lesion basis was too small to evaluate publication bias; however, publication bias was indicated (Deeks' Funnel Plot Asymmetry Test, P=0.01) in the use of ^{68}Ga-SSTR PET for diagnosing NET on a per-patient basis.

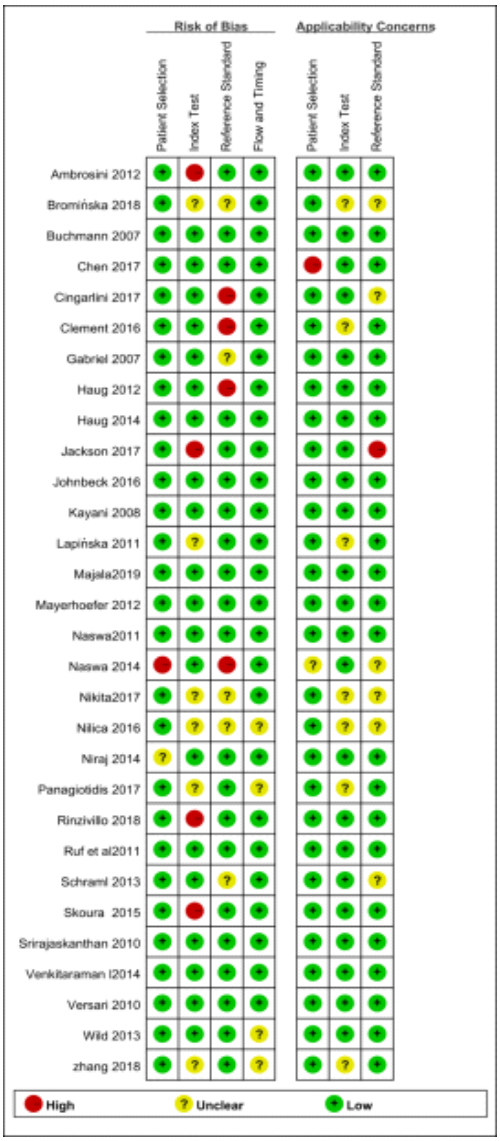

Figure 2. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies. Different colours (green, red and yellow) and symbols (' + ', '-' and '?') were used in the figure to indicate low risk bias, high risk bias and unclear, respectively.

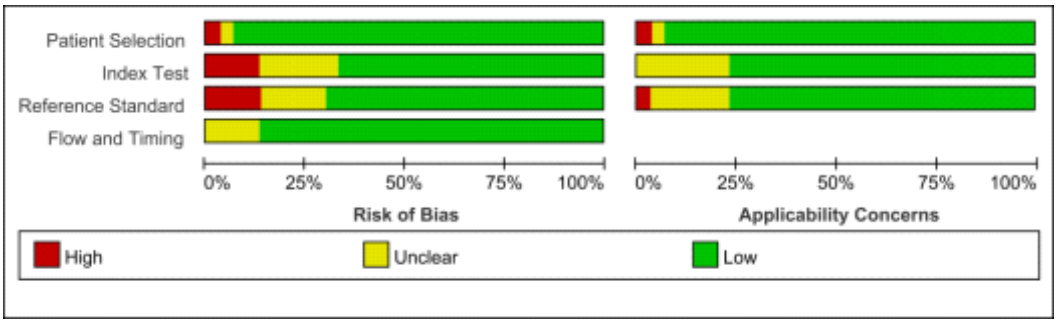

Figure 3. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.

The influence of the examination method on patient or lesion management

The diagnostic value of the outcomes of ^{68}Ga-SSTR PET or PET/CT in the 20 included articles in the meta-analysis are shown in Table 2. The sensitivity syntheses for ^{68}Ga-SSTR, ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC and ^{18}F-FDG PET or PET/CT in the diagnosis of NET, calculated on a per-patient basis, were 0.92 (95% CI: 0.89-0.95), 0.95 (95% CI: 0.89-0.97), 0.92 (95% CI: 0.86-0.95), 0.87 (95% CI: 0.80-0.92) and 0.70 (95% CI: 0.41-0.89), and the syntheses specificities were 0.91 (95% CI: 0.83-0.95), 0.91 (95% CI: 0.77-0.97), 0.88 (95% CI: 0.80-0.93), 0.90 (95% CI: 0.41-0.99) and 0.97 (95% CI: 0.70-1.00), respectively.

Due to insufficient data, it was impossible to perform a meta-analysis on a per-lesion basis for ^{68}Ga-DOTATATE and ^{18}F-FDG PET or PET/CT, but the sensitivity syntheses for ^{68}Ga-SSTR, ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC PET or PET/CT in the diagnosis of NET were 0.95 (95% CI: 0.86-0.98), 0.93 (95% CI: 0.82-0.98) and 0.964 (95% CI: 0.911-0.990), and the pooled specificities were 0.93 (95% CI: 0.83-0.97), 0.96 (95% CI: 0.88-0.99) and 0.762 (95% CI: 0.605-0.879), respectively. The AUC of ^{68}Ga-SSTR (Figure 4), ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC and ^{18}F-FDG PET or PET/CT on a per-patient basis were 0.96 (95% CI: 0.94-0.98), 0.98 (95% CI: 0.96-0.99), 0.96 (95% CI: 0.94-0.97), 0.89 (95% CI: 0.86-0.92) and 0.94 (95% CI: 0.92-0.96), respectively.

The pooled sensitivities of ^{68}Ga-SSTR PET/CT were 0.923 (95% CI: 0.884-0.952), 0.902 (95% CI: 0.862-0.934) and 0.578 (95% CI: 0.482-0.669) in the G1, G2 and G3 groups based on patients with NET, respectively. The pooled sensitivities of ^{18}F-FDG PET/CT were 0.378 (95% CI: 0.319-0.440), 0.554 (95% CI: 0.492-0.615) and 0.712 (95% CI: 0.633-0.783) in the G1, G2 and G3 groups based on patients with NET, respectively. The pooled specificities and DOR of ^{68}Ga-SSTR and ^{18}F-FDG PET/CT in three groups of NET shown in Table 3. The ROC curve could not be used to evaluate the diagnostic efficacy of ^{68}Ga-SSTR and ^{18}F-FDG PET/CT in G1, G2, and G3 due to insufficient data obtained.

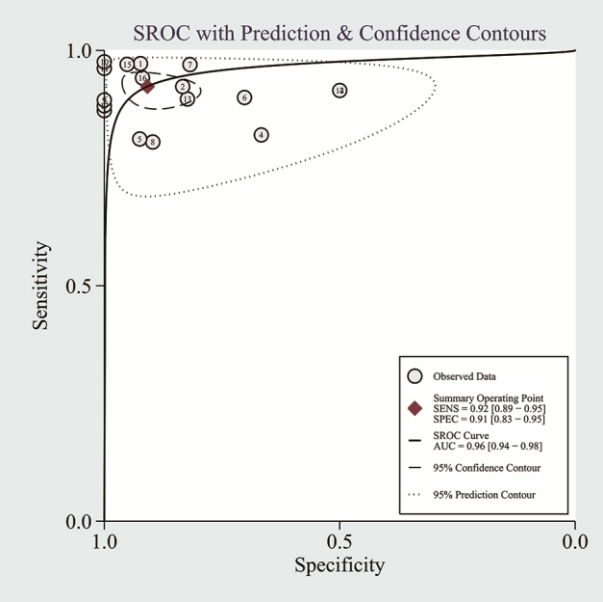

Figure 4. The SROC curves for ^{68}Ga-SSTR PET or PET/CT on a per-patient basis. The AUC of ^{68}Ga-SSTR PET or PET/CT on a per-patient basis were 0.96 (95% CI: 0.94-0.98), The pool sensitivity and specificity for ^{68}Ga-SSTR PET or PET/CT were 0.92 (95% CI: 0.89-0.95) and 0.91 (95% CI: 0.83-0.95), respectively.

Table 2. *Diagnostic performance for ^{68}Ga-SSTR PET/CT and ^{18}F-FDG PET/CT on a per-patient basis and per-lesion basis.*

Modality	^{68}Ga-SSTR	^{68}Ga-DOTATOC	^{68}Ga-DOTATATE	^{68}Ga-DOTANOC	^{18}F-FDG
Per-patient					
Sensitivity (95%CI)	0.92(0.89-0.95)	0.95(0.89-0.97)	0.92(0.86-0.95)	0.87(0.80-0.92)	0.70(0.41-0.89)
Specificity (95%CI)	0.91(0.83-0.95)	0.91(0.77-0.97)	0.88(0.80-0.93)	0.90(0.41-0.99)	0.97(0.70-1.00)
DOR (95%CI)	119(51-282)	185(37-913)	85(29-248)	62(6-676)	67(7-612)
AUC	0.96(0.94-0.98)	0.98(0.96-0.99)	0.96(0.94-0.97)	0.89(0.86-0.92)	0.94(0.92-0.96)
Per-lesion					
Sensitivity (95%CI)	0.95(0.86-0.98)	0.93(0.82-0.98)	-	0.964（0.911-0.990）	-
Specificity (95%CI)	0.93(0.83-0.97)	0.96(0.88-0.99)	-	0.762（0.605-0.879）	-
DOR (95%CI)	229(43-1205)	353(34-3613)	-	95.260（26.516-342.23）	-
AUC (95%CI)	0.98(0.96-0.99)	0.99(0.97-0.99)	-	0.50	-

DOR, diagnostic odds ratios, AUC, area under curve, CI, confidence intervals.

Heterogeneity exploration and meta-regression analysis

The per-patient-based pooled sensitivity and specificity values for ^{68}Ga-SSTR, ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE and ^{18}F-FDG with PET or PET/CT were highly heterogeneous. However, the per-patient-based pooled sensitivity of ^{68}Ga-DOTANOC and specificity of ^{18}F-FDG were not statistically heterogeneous, with I2 values of 47.97 and 9.43, respectively. The detailed heterogeneity results of the per-lesion-based method are shown in Table 4.

To detect the sources of heterogeneity, a meta-regression was carried out for the studies that analyzed ^{68}Ga-SSTR PET or PET/CT for detecting NET on a per-patient basis. The meta-regression analysis content included study design (prospective vs retrospective), imaging modality (PET vs PET/CT), blinded (yes vs no) and sample size (greater than 30 vs not). The meta-regression results for sensitivity and specificity are shown in Table 5, and the univariate meta-regression and subgroup analyses are illustrated in Figure 5. Study design, imaging modality and blinding may have led to the heterogeneity of the sensitivity analysis of ^{68}Ga-SSTR PET or PET/CT for detecting NET on a per-patient basis (P<0.05). Additionally, blinding may have caused heterogeneity in the specificity analysis of ^{68}Ga-SSTR PET or PET/CT for detecting NET on a per-patient basis (P<0.05).

Table 3. *Diagnostic performance for ^{68}Ga-SSTR PET/CT and ^{18}F-FDG PET/CT in G1, G2 and G3 of NET, patient-based and lesion-based analysis.*

Grade	G1(ki67≤2%)	G2(20%≤ki67>2%)	G3(ki67＞20%)
Per-patient (^{68}Ga-SSTR)			
Sensitivity (95%CI)	0.923(0.884-0.952)	0.902(0.862-0.934)	0.578(0.482-0.669)
Specificity (95%CI)	0.923(0.884-0.952)	Not estimable	0.536(0.412-0.657)
DOR (95%CI)	22.808(2.935-177.22)	4.778(1.234-18.506)	1.671(0.272-10.271)
Per-lesion (^{68}Ga-SSTR)			
Sensitivity (95%CI)	0.972(0.935-0.991)	0.532(0.458-0.605)	0.552(0.479-0.624)
Specificity (95%CI)	Not estimable	Not estimable	Not estimable
DOR (95%CI)	34.383(1.829-646.43)	1.966(0.025-157.49)	0.812(0.007-87.875)
Per-patient (^{18}F-FDG)			
Sensitivity (95%CI)	0.378(0.319-0.440)	0.554(0.492-0.615)	0.712(0.633-0.783)
Specificity (95%CI)	Not estimable	Not estimable	Not estimable
DOR (95%CI)	0.320(0.109-0.934)	2.085(0.722-6.020)	1.461(0.147-14.487)

DOR, diagnostic odds ratios; CI, confidence intervals; G1,Grade 1 or low grade,Ki-67 index of 2% or lower; G2, Grade 2 or moderate-grade,Ki-67 index between 3% and 20%; G3,Grade 3 or high grade,Ki-67 index higher than 20%;Not estimable,The combination of effect indicators cannot be calculated due to insufficient data obtained.

Table 4. *Assessment of heterogeneity and threshold effect of included articles.*

Modality	^{68}Ga-SSTR	^{68}Ga-DOTATOC	^{68}Ga-DOTATATE	^{68}Ga-DOTANOC	^{18}F-FDG
Per-patient (Sensitivity)					
I^2 (95%CI)	74.97 (63.13 - 86.81)	62.72 (32.13 - 93.31)	88.12 (80.09 - 96.15)	47.97 (0.00 - 100.00)	92.83(87.48-98.19)
Q*	63.92	16.09	42.10	5.77	41.86
df	16	6.00	5.00	3.00	3.00
P value	0.00	0.01	0.00	0.12	0.00
Per-patient (Specificity)					
I^2 (95%CI)	77.99 (67.94 - 88.05)	56.11 (19.07 - 93.15)	83.80 (71.91 - 95.70)	92.43 (86.69 - 98.17)	9.43(0.00-100.00)
Q*	72.71	13.67	30.87	39.63	3.31
df	16	6.00	5.00	3.00	3.00
P value	0.00	0.03	0.00	0.00	0.35

(continued)

Per-lesion (Sensitivity)					
I^2 (95%CI)	96.96 (95.79 - 98.13)	97.77 (96.86 - 98.69)	-	-	-
Q*	230.28	224.52	-	-	-
df	7.00	5.00	-	-	-
P value	0.00	0.00	-	-	-
Per-lesion (Specificity)					
I2（95%CI）	95.56 (93.64 - 97.47)	95.54 (93.28 - 97.81)	-	-	-
Q*	157.54	112.21	-	-	-
df	7.00	5.00	-	-	-
P value	0.00	0.00	-	-	-

I^2,I-squared(inconsistency); CI, confidence intervals;df, degree of freedom.

Table 5. *Meta regression results of sensitivity and specificity for ^{68}Ga-SSTR PET or PET/CT in NET.*

Parameter	Category	Studies(n)	Sensitivity (95%CI)	P1	Specificity (95%CI)	P2
Prodesign	Yes	6	0.92(0.88-0.97)	0.00	0.98(0.94-1.00)	0.10
	No	11	0.92(0.89-0.96)		0.87(0.79-0.95)	
Size30	Yes	16	0.92(0.90-0.95)	0.71	0.91(0.85-0.97)	0.23
	No	1	0.93(0.78-1.00)		0.86(0.48-1.00)	
Blinded	Yes	11	0.91(0.87-0.95)	0.00	0.88(0.79-0.97)	0.04
	No	6	0.94(0.91-0.97)		0.93(0.88-0.99)	
Res	Yes	14	0.92(0.89-0.95)	0.02	0.91(0.84-0.97)	0.93
	No	3	0.93(0.87-1.00)		0.93(0.80-1.00)	

Prodesign,Prospective design; Size30,Study size greater than 30; Res,Resolution of PET/CT;CI, confidence intervals.

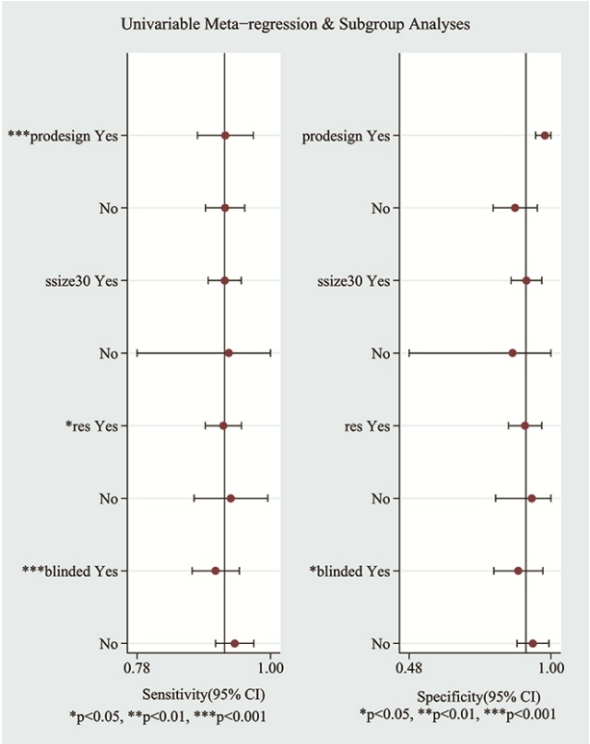

Figure 5. Univariate meta-regression and subgroup analysis. Study design, imaging modality and blinding may have led to the heterogeneity of the sensitivity analysis of ^{68}Ga-SSTR PET or PET/CT for detecting NET on a per-patient basis (P<0.05). Additionally, blinding may have caused heterogeneity in the specificity analysis of ^{68}Ga-SSTR PET or PET/CT for detecting NET on a per-patient basis (P<0.05).

Discussion

Neuroendocrine tumours comprise a group of unique tumours that are defined in various ways [50, 51]. In terms of clinical features, NET are usually considered inert but have malignant tendencies and may produce hormones that produce some syndromes (e.g., carcinoid syndrome) [4]. Neuroendocrine tumours can be located in nearly every organ; however, they are most commonly detected in the gastrointestinal tract, pancreas, and lungs [1, 4]. The clinical manifestations and outcomes of and therapies for NET mainly depend on the organ of origin, hormonal excretions, and tumour grade stage, for which the overwhelming majority of imaging systems offer inestimable diagnostic information [4].

Several prospective articles have reported the sensitivity and specificity of ^{68}Ga-SSTR PET or PET/CT for patients with NET. Schraml and his team (2013) designed a study to compare the diagnostic accuracy of ^{68}Ga-DOTATOC PET/CT and whole-body magnetic resonance imaging (WBMRI) in patients with NET [34]. According to their studies, ^{68}Ga-DOTATOC PET/CT had significantly higher sensitivity than WBMRI for metastatic lesions of lymph nodes (100% vs 73%; P< 0.0001) and lung lesions (100% vs 87%; P=0.0233) with respect to lesion-based positive rates; however, WBMRI had strongly higher positive rates in liver (99% vs 92%; P<0.0001) and skeleton lesions (96% vs 82%; P<0.0001) [34]. Therefore, Schraml et al. (2013) revealed that ^{68}Ga-DOTATOC PET/CT and WBMRI had comparable entire lesion-based positive rates for metastatic correlations in NET [34]. Another prospective study evaluated 51 patients with NET with nuclear medicine imaging using ^{68}Ga-DOTATATE PET and ^{111}In octreotide scanning [26]. They indicated that the sensitivity and specificity of ^{68}Ga-DOTATATE PET were 87.2% and 100%, respectively, for patients with NET and that the true positive rate was 74.3% [26]. In addition, ^{68}Ga-DOTATATE PET can detect additional lesions and may be used to modify tumour management in most cases when the ^{111}In octreotide scan was negative or equivocal in patients with NET [26]. Łapińska et al. (2011) also assessed the diagnostic performance of ^{68}Ga-DOTATATE PET/CT in the visualization of SSTR and the identification of new lesions, and they described that the sensitivities were 90% and 70.2%, respectively [29]. Although these studies indicated that ^{68}Ga-SSTR PET or PET/CT has high diagnostic performance in NET, their sensitivities and specificities are inconsistent.

To address the discrepancies described in the above studies, we performed a meta-analysis designed to compare the diagnostic performances of ^{68}Ga-SSTR and ^{18}F-FDG PET or PET/CT in detecting NET on per-patient and -lesion bases. Our results showed that ^{68}Ga-SSTR PET or PET/CT has a high sensitivity (92%) and specificity (91%) for evaluation of NET based on patient. The pooled sensitivity and specificity on a per-lesion basis of ^{68}Ga-SSTR PET or PET/CT were 95% and 93%, respectively. In addition, this meta-analysis compared ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC on a per-patient basis. Among the three imaging agents, ^{68}Ga-DOTANOC (DOR:62, AUC:0.89) has slightly worse diagnostic efficiency than ^{68}Ga-DOTATOC (DOR:185, AUC:0.98) and ^{68}Ga-DOTATATE (DOR:85, AUC:0.96). There were no significant differences between ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE.

A previous meta-analysis [15] reported and compared the diagnostic roles of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE PET in NET on a per-patient basis and indicated that the pooled sensitivities were 93% and 96% and the specificities were 85% and 100%, respectively. The study also indicated that the AUC were 0.96 and 0.98, respectively. These results are consistent with ours. Besides, the article [15] has several shortcomings, for example, an insufficient sample size, unacceptably large statistical heterogeneity and no discussion of the sources of heterogeneity. Another meta-analysis evaluated the role of ^{68}Ga-SSTR PET or PET/CT in detecting NET in 16 studies [14]. The sensitivity and specificity of ^{68}Ga-SSTR PET or PET were 93% and 91%, respectively [14]. Nevertheless, only the data from 5 studies could be completely extracted to calculate the sensitivity and specificity. In addition, the study did not perform meta-regression or subgroup analysis to discuss the sources of heterogeneity because it was too significant. In our meta-analysis, the pooled diagnostic efficacy of ^{68}Ga-SSTR PET or PET/CT was excellent and satisfying. Our results were also consistent with the results of other well-designed studies.

Our study also revealed that the pooled sensitivity, specificity, DOR and AUC on a per-patient basis of ^{18}F-FDG PET or PET/CT were 0.70, 0.97, 67 and 0.94, respectively. Because only one study analysed the data from ^{18}F-FDG PET or PET/CT on a per-lesion basis, it was impossible to calculate these parameters. Naswa et al. (2014) [11] investigated the diagnostic performance of ^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT for patients with gastroenteropancreatic neuroendocrine tumours (GEPNET). In patient-based analysis, the sensitivity and specificity of ^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT for detecting GEPNET were 91.4%, 50% and 42.5%, 100%, respectively. In lesion-based analysis, the sensitivity and specificity of ^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT for detecting GEPNET were 94.2%, 87.5% and 25.7%, 100%, respectively. The role of ^{68}Ga-DOTANOC PET/CT and ^{18}F-FDG PET/CT seems complimentary, because ^{68}Ga-DOTANOC PET/CT can overcome the low sensitivity of ^{18}F-FDG PET/CT, while ^{18}F-FDG PET/CT can overcome the low specificity of ^{68}Ga-DOTANOC PET/CT when the lesions do not accumulate ^{68}Ga-DOTANOC [11]. Chen et al. (2017) [37] analyzed the diagnostic accuracy of ^{68}Ga-DOTATOC and ^{18}F-FDG PET/CT in identifying the primary foci in Taiwanese patients with clinically suspected NET and NET from unknown primary sites. Their results showed that the overall sensitivities of ^{68}Ga-DOTATOC, ^{18}F-FDG, and conventional workup were 88%, 41%, and 53%, respectively, whereas the specificities were 100%, 100%, and 68%, respectively. Based on their data, they concluded that ^{68}Ga-DOTATOC was more sensitive than ^{18}F-FDG, and more specific than the conventional workup [37]. Additionally, one study proposed that ^{68}Ga-DOTATOC should be considered the primary imaging modality for clinically suspected NET or NET from unknown primary sites. If positive results are obtained on ^{68}Ga-DOTATOC, ^{18}F-FDG PET/CT is not required [37]. However, ^{18}F-FDG PET/CT should be considered to further screen for primary NET foci in patients with negative findings on ^{68}Ga-DOTATOC [37]. Such a strategy

would result in increased diagnostic efficiency as well as time and cost reductions while keeping radiation exposures as low as reasonably possible [37]. Therefore, the two examinations are complementary rather than substitutive in clinical practice.

Although our results believe that ^{68}Ga-SSTR scans are highly sensitive, not full range of NET (poorly/moderate/well-differentiated) can be positively identified. For that reason, our research also assessed the diagnostic efficacy of ^{68}Ga-SSTR and ^{18}F-FDG PET/CT at different pathological grading (G1, G2, G3) of NET, suggesting that the combined efficacy of the two imaging agents presented a flip-flop phenomenon. In G1,G2 and G3, the sensitivities of ^{68}Ga-SSTR were 92.3%, 90.2% and 57.8%, and that of ^{18}F-FDG were 37.8%, 55.4% and 71.2%, respectively. Due to lack of sufficient data, it is not possible to calculate the specificity by merging. Panagiotidis et al. (2017) [45] had compared the impact of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT on clinical management in patients with NET. Their study demonstrated that routine use of both ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT is not recommended for G1 NET. In this NET subgroup the clinical impact was influenced predominately by the ^{68}Ga-DOTATATE study, which Panagiotidis et al. (2017) [45] suggested should be performed solely. Our results also proved ^{68}Ga-SSTR has more higher diagnostic performance in G1 NET than ^{18}F-FDG, while, in G3 the opposite is true.

Neuroendocrine tumours with poor differentiation, a high grade and rapid proliferation have a decreased expression of somatostatin receptor expression and, therefore, the ^{68}Ga-DOTATOC scan may be negative, while ^{18}F-FDG imaging may be positive because of the significant increase in glycolytic metabolism [45]. The presence of increased glucose in NET highlights an increased propensity for invasion and metastasis, and ^{18}F-FDG PET/CT accordingly has higher sensitivity in delineating disease extent, especially in aggressive and high-grade tumors [52]. In the G3 NET group, ^{18}F-FDG results in patients with higher Ki67 index values reflect a high level of glycolytic metabolism in high-risk patients with aggressive disease and poorer prognosis. However, ^{68}Ga-DOTATATE should also be considered in G3 subgroup, especially in the event of relapse on chemotherapy regimen, as the somatostatin receptor positivity makes peptide receptor radionuclide therapy a potential therapeutic option.

This study found that the positive rate of ^{68}Ga-SSTR (90.2%) in detecting G2 NET lesions was still higher than that of ^{18}F-FDG (55.4%). Has et al. (2014) [53] have concluded that the uptake of ^{68}Ga-SSTR is higher in G2a (Ki67, 3%-9%) than in G2b (Ki67,10%-20%) tumors. Their data showed that the uptake of ^{68}Ga-SSTR in G2a was significantly higher than that of G2b and significantly higher than that of ^{18}F-FDG. On the contrary to ^{68}Ga-SSTR, the uptake of ^{18}F-FDG was not statistically different between G2a and 2b. Additionally, in G2b, there was no statically significant difference between the uptake of ^{18}F-FDG and ^{68}Ga-SSTR PET/CT. These data demonstrate that GEPNET with a Ki67 lower than 10% may be more suited to fall in the low-grade category in terms of SSTR positivity, which can alter the treatment [53]. Gallium-68-SSTR uptake values of G2b are statistically lower than those of G2a patients, suggesting that G2b (Ki67, >10%) patients may be considered as higher grade GEPNET [53]. Our study hadn't evaluated G2a and G2b because of the limited number of patients.

The sensitivities and specificities for ^{68}Ga-SSTR PET or PET/CT were highly heterogeneous, so we used a random-effects model to complete data synthesis and analysis. Additionally, exploring the source of heterogeneity is an important part of the meta-analysis. Compared with previous meta-analyses, our study has rich data and unique advantages. In addition, the heterogeneity tests, meta-regression analyses and subgroup analyses from these studies were investigated, and factors leading to heterogeneity were found in this study. Different study designs, different imaging modalities, whether the study was blinded and different threshold settings may have led to heterogeneity.

In this meta-analysis, publication bias was found in the use of ^{68}Ga-SSTR PET for diagnosing NET on a per-patient basis. The following categories may be the cause of publication bias: positive results are more likely to be published; the methodological quality of the included studies is poor; negative results are difficult for editors to accept; research is influenced by funding sources.

The shortcoming of this meta-analysis is that the number of articles of ^{18}F-FDG PET in NET is too small for pooling the per-lesion-based sensitivity, specificity, DOR and AUC. In the article on pathological staging of NET, the true negative data of ^{68}Ga-SSTR and ^{18}F-FDG were too little to be combined with specificity. There is also no subgroup analysis of G2 in this paper. Therefore, a larger sample size, better quality datasets and multicentre studies are needed to evaluate the diagnostic performance of ^{68}Ga-SSTR and ^{18}F-FDG PET/CT in G1, G2 and G3 NET.

Our meta-analysis concluded that ^{68}Ga-SSTR PET was highly sensitive and had a greater diagnostic value than ^{18}F-FDG PET for patients with NET. Fluorine-18-FDG PET, however, had significant specificity than ^{68}Ga-SSTR PET for patients with NET. The ^{68}Ga-SSTR has high sensitivity in G1/G2 NET, while ^{18}F-FDG has a low positive rate. In G3 NET, however, the opposite is true. Therefore, the ^{68}Ga-SSTR PET and ^{18}F-FDG PET modalities are complementary rather than substitutive in clinical practice.

Authors' contributions

XL and NL were involved in data management and statistics, and drafted the manuscript. TJ and HWX verified the extracted data following the literature search, monitored the study and drafted the manuscript. QLR designed the current study. TJ and ZS conducted the searches and performed statistical analysis. XL and NL performed extracted the data and contributed to quality assessment. All authors contributed to drafting and revising the manuscript and all authors read and approved the final manuscript.

The authors declare that they have no conflicts interests.

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