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META-ANALYSIS

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Detection rate of unknown primary tumour by using somatostatin receptor PET/CT in patients with metastatic neuroendocrine tumours: a meta-analysis

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Abstract

Purpose The high diagnostic performance of somatostatin receptor positron emission tomography with computed tomography (PET/CT) in neuroendocrine tumours (NETs) was demonstrated by several articles. However, only some studies evaluated the detection rate (DR) of this imaging method in patients with metastatic NETs and unknown primary tumours (CUP-NETs). Therefore, we aimed to perform a meta-analysis to add evidence-based data in this setting.

Methods A comprehensive computer literature search of studies listed in PubMed/MEDLINE, EMBASE, and Cochrane library databases through December 2018 and regarding the use of somatostatin receptor PET/CT in patients with CUP-NETs was carried out. Pooled DR of CUP-NETs by using somatostatin receptor PET/CT was calculated. A pooled analysis evaluating the percentage of change of management by using somatostatin receptor PET/CT in these patients was also performed.

Results Twelve studies on the use of somatostatin receptor PET/CT in detecting CUP-NETs in 383 metastatic patients were included. The meta-analysis of all these studies provided the following DR on a per patient-based analysis: 56% (95% confidence interval (95% CI): 48–63%). Moderate heterogeneity among the selected studies was found ($I^2 = 50\%$), whereas a significant publication bias was excluded by Egger's test ($p = 0.45$). The most common primary tumour sites were the bowel and the pancreas. A change of management by using somatostatin receptor PET/CT was demonstrated in 20% (95% CI: 10–33%) of patients with CUP-NET.

Conclusions Somatostatin receptor PET/CT is very useful in detecting CUP-NETs in patients with metastatic disease. More studies on the change of management by using this imaging method in this setting are needed.

Keywords PET · Somatostatin · Neuroendocrine · Unknown primary · CUP-NET.

Introduction

In cancer of unknown primary (CUP), metastases are clinically and histologically confirmed, but the primary

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tumour site remains elusive after extensive work-up. The prevailing histologies in CUP are adenocarcinomas and undifferentiated carcinomas, whereas squamous cell carcinomas, neuroendocrine tumours (NETs), and rare histologies account for the remaining 10% [1].

NETs are mostly relatively indolent malignancies but a significant number of these neoplasms has metastatic disease at diagnosis (mainly to the liver). An overall prevalence of metastatic NETs with unknown primary (CUP-NETs) of ~11–22% has been documented [2]. Since surgical and medical management as well as prognosis of NETs depend on individual tumour characteristics, besides tumour staging and grading, every effort should be made to obtain localization of CUP-NETs even in presence of metastatic disease [2]. In fact, localization and resection of CUP-NETs is associated with improvement of progression free survival and overall survival [3], and the choice of treatment depends on the location of the primary tumour [2]. Therefore, a continuum of investigations to identify the CUP-NETs is warranted. In patients with potentially resectable metastatic disease, the identification of CUP-NET is of outmost importance as it offers the best option for "cure". Before patients are considered as suitable candidates for surgery, a multidisciplinary team assessment, clinical evaluation, biochemical markers assay and imaging studies (both morphological and functional) may be helpful to identify CUP-NETs [2].

Positron emission tomography (PET) is a functional imaging method that is extensively used in oncology. Hybrid techniques using the combination of PET with computed tomography (PET/CT) or magnetic resonance imaging (PET/MRI) allow to obtain both functional and morphological data even in NETs [4–6].

Somatostatin analogues radiolabelled with the positron emitting radionuclide Gallium-68 (^{68}Ga) may be used as radiotracers for PET imaging in NETs. These radiotracers may target the transmembrane somatostatin receptors (SSTRs), which are usually overexpressed in NETs [4–6]. Several somatostatin analogues may be used for somatostatin receptor PET (i.e., ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC) with some differences in the affinity profile for the different SSTR subtypes without significant impact in lesion detection rate (DR) [4–6].

Physical advantages of PET/CT or PET/MRI tomographs combined with the improved pharmacological properties or radiolabelled somatostatin analogues increase the DR of NETs compared with conventional imaging methods, allowing the detection of smaller lesions and/or lesions with moderate SSTRs expression [4–6].

To date, several evidence-based articles demonstrated the high diagnostic performance and impact of somatostatin receptor PET/CT in NETs [7–11]. However, only some studies evaluated the DR of CUP-NET by using this imaging method in patients with metastatic disease [12]. Therefore, we aimed to perform a systematic review and meta-analysis to add evidence-based data in this setting.

Methods

Reporting of this systematic review and meta-analysis conforms to the "Preferred Reporting Items for a Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies" (PRISMA-DTA statement), which describes an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses of diagnostic studies [13–15].

Search strategy

Two authors performed a comprehensive computer literature search of PubMed/MEDLINE, EMBASE, and Cochrane library databases to find relevant retrospective or prospective published articles on the DR of CUP by using somatostatin receptor PET/CT in patients with metastatic NETs.

A search algorithm based on a combination of these terms was used: (A) "neuroendocrine" AND (B) "unknown" AND (C) "PET" or "positron emission tomography". No beginning date limit was used. The search was updated until 30th December 2018. No language restriction was used. To expand our search, references of the retrieved articles were also screened for additional studies.

Study selection

Studies or subsets of studies investigating the DR of CUP by using somatostatin receptor PET/CT in patients with metastatic NET histologically proved were eligible for inclusion in the qualitative (systematic review) and quantitative analysis (meta-analysis). The exclusion criteria were: (a) articles not within the field of interest of this review; (b) review articles, editorials or letters, comments, conference proceedings; (c) case reports or small case series (less than patients); (d) articles with insufficient data to reassess the DR of CUP-NET by using somatostatin receptor PET/CT; (e) articles with possible patient data overlap.

Three researchers independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. Articles were rejected if they were clearly ineligible. The same three researchers then independently reviewed the full-text version of the remaining articles to assess their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data extraction

For each study potentially eligible for the meta-analysis, information was collected concerning basic study (authors, year of publication, country of origin, study design), patient characteristics (type and number of patients evaluated, mean age, sex ratio, site, and histopathological grading of metastatic disease at initial diagnosis), technical aspects (radiotracer used, hybrid imaging modality, radiotracer injected activity, time interval between radiotracer injection and image acquisition, image analysis, reference standard, and comparison with other imaging methods), DR of CUP-NET (on a patient-based analysis), sites of CUP-NET (on a lesion-based analysis), and percentage of change of management by using somatostatin receptor PET/CT.

Quality assessment

The overall quality of the studies included in the systematic review and meta-analysis was critically appraised based on the revised "Quality Assessment of Diagnostic Accuracy Studies" tool (QUADAS-2) [16]. This tool comprises four domains: patient selection, index test, reference standard, and flow and timing. Each domain was assessed in terms of risk of bias, and the first three domains were also assessed in terms of concerns regarding applicability [16].

Statistical analysis

The DR of somatostatin receptor PET/CT was defined as the ratio between the number of patients with CUP-NET with known metastases detected by PET/CT and the total number of CUP-NET patients who underwent the scan.

Pooled analyses of DR of CUP-NET detected by somatostatin receptor PET/CT and percentage of change of management obtained by using somatostatin receptor PET/CT were performed using data retrieved from the selected studies. Subgroup analyses taking into account study design and technical aspects were planned.

A random-effects model was used for statistical pooling of the data, taking into account the heterogeneity between studies. The different weight of each study in the pooled analysis was related to the different sample size. Pooled data were presented with their respective 95% confidence interval (95% CI) values, and data were displayed using plots.

Heterogeneity was estimated by using the *I*-square index (I^2), which describes the percentage of variation across studies that is owing to heterogeneity rather than chance [17].

Publication bias was assessed through the Egger's test [18].

Statistical analyses were performed using the StatsDirect software version 3 (StatsDirect Ltd., Cambridge, UK).

Results

Literature search

Literature search results are reported in Fig. 1. The comprehensive computer literature search from PubMed/MEDLINE, EMBASE, and Cochrane library database revealed 128 articles. Reviewing titles and abstracts, 111 articles were excluded: 89 because not in the field of interest of this review, 11 as reviews, editorials or letters, 11 as case reports or small case series (<5 patients). Seventeen articles were selected and retrieved in full-text version [19–35]. Subsequently, five full-text articles were excluded owing to insufficient data to reassess the DR of CUP-NET by using somatostatin receptor PET/CT [31–35]. No additional studies were found screening the references of these articles. Finally, 12 articles including data on the DR of CUP by somatostatin receptor PET/CT in 383 patients with metastatic NETs were eligible for the qualitative analysis (systematic review) and the quantitative analysis (meta-analysis) [19–30]. The characteristics of the studies selected for the systematic review are presented in Table 1–3. Overall quality assessment of the studies is reported in Fig. 2.

Qualitative analysis (systematic review)

Basic study and patient characteristics

Using the database search, 12 full-text articles including data on the DR of CUP by somatostatin receptor PET/CT in 383 patients with metastatic NETs were selected (Table 1) [19–30]. All the selected articles were published in the last nine years. Several countries from Europe, Asia, North, and South America were represented. Two-thirds of the studies were retrospective and most of the articles were single-centre studies (92%).

Mean age of the patients included in these studies ranged from 46 to 65 years. About the sex ratio, the percentage of male patients in the selected studies ranged from 36 to 83%. Liver, lymph nodes, bone, and lungs were the most frequent sites of metastatic disease at initial diagnosis in patients with CUP-NET. Most of metastatic sites were well or moderately differentiated NETs at biopsy.

Technical aspects

Heterogeneous technical aspects among the included studies were found about somatostatin receptor PET/CT (Table 2). The radiotracer used was ^{68}Ga-DOTATATE in 6 (50%) studies, ^{68}Ga-DOTATOC in 3 (25%) studies and ^{68}Ga-DOTANOC in 3 (25%) studies. The hybrid imaging modality was PET/CT in 100% of the studies by using low-dose

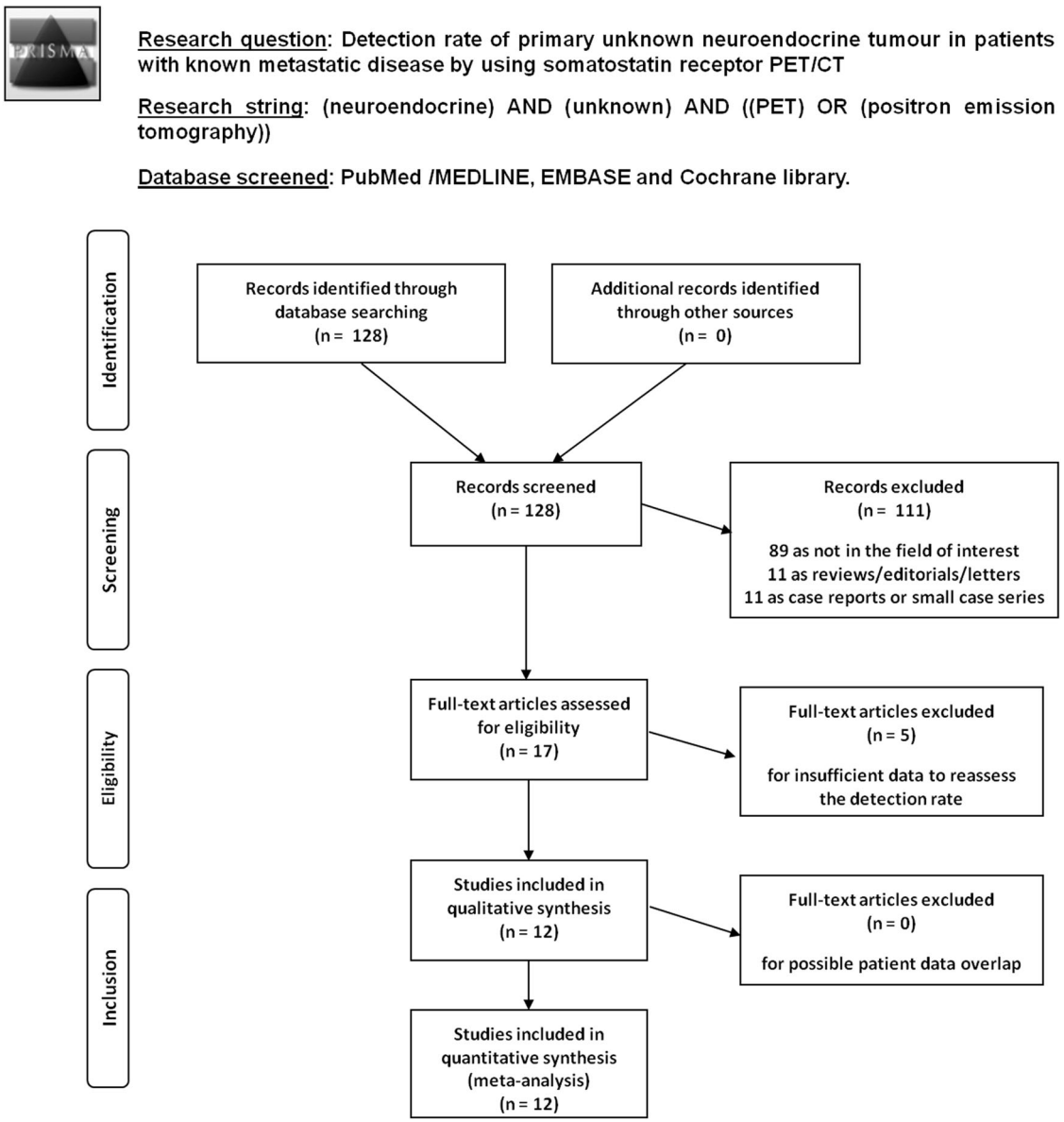

Fig. 1 Flow chart of the search for eligible studies on the detection rate of CUP-NET by somatostatin receptor PET/CT

or contrast-enhanced CT. Mean injected radiotracer activity and time interval between radiotracer injection and image acquisition were quite different among the included studies. The PET image analysis was performed by using qualitative (visual) analysis in all studies and additional semi-quantitative analysis through the calculation of the maximal standardized uptake values (SUV_{max}) in most of the studies (92%). At 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.

Histology or further imaging or clinical/biochemical follow-up was considered as reference standard in the included studies (composite reference standard).

Somatostatin receptor PET/CT findings were compared with conventional imaging findings, somatostatin receptor scintigraphy or fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET/CT findings in some articles.

Main findings

Main findings of the included studies are listed in Table 3. Overall, all articles demonstrated the usefulness of somatostatin receptor PET/CT in detecting CUP-NET in patients with metastatic disease with a DR ranging from 29 to 83%. The site of CUP-NET detected by somatostatin receptor PET/CT were pancreas or bowel in most of the cases.

Table 1 Basic study and patient characteristics

Authors	Year	Country	Study design	Type of patients evaluated	No. of patients with metastatic CUP-NET performing somatostatin receptor PET	Mean age and range (years) of patients with metastatic CUP-NET	Male/female ratio (% male) of patients with metastatic CUP-NET	Metastatic disease sites at initial diagnosis in patients with CUP-NET	Histopathological grade from biopsy of metastatic sites
Sampathirao et al. [19]	2017	India	Retrospective single-centre	Patients with metastatic CUP-NET scheduled for PRRT	51	48 (22–74)	25/26 (49%)	Liver (94%), lymph node (49%), bone (24%), lung (6%), other (8%)	Well or moderately differentiated: 92%; poorly differentiated or undifferentiated: 8%
Menda et al. [20]	2017	USA	Prospective single-centre	Patients with metastatic CUP-NET who underwent somatostatin receptor PET/CT for primary tumour localization	40	55 ± 12 (20–75)	23/17 (57%)	Liver (73%), lymph nodes (20%), bone (15%), lung (13%), other (12%)	low grade: 33%; intermediate grade: 42%; high grade: 20%; unknown: 5%
Kazmierczak et al. [21]	2017	Germany	Retrospective single-centre	Patients with metastatic CUP-NET who underwent somatostatin receptor PET/CT for primary tumour localization	38	63 ± 10 (34–76)	27/11 (71%)	Liver (61%), lymph nodes (13%), lung (5%), other (21%)	low grade: 47%; intermediate grade: 53%; high grade = 0%
Sadowski et al. [22]	2016	USA	Prospective single-centre	Patients with known/suspicious NET who underwent somatostatin receptor PET/CT for staging (including a subgroup of patients with metastatic CUP-NET)	14	NR	NR	NR	NR
Pruthi et al. [23]	2016	India	Retrospective single-centre	Patients with metastatic CUP-NET who underwent somatostatin receptor PET/CT for primary tumour localization	68	54.9 ± 10.7 (31–78)	45/23 (66%)	Liver (74%), lymph nodes (15%), mesentery (9%), bone (1%), other (1%)	Low grade: 24%; intermediate grade: 15%; high grade: 7%; unknown: 54%
Nakamoto et al. [24]	2015	Japan	Retrospective single-centre	Patients with known/suspicious NET who underwent somatostatin receptor PET/CT for staging (including a subgroup of patients with metastatic CUP-NET)	14	56 (28–80)	5/9 (36%)	Liver (64%), lymph nodes (22%),bone (14%)	NR
Alonso et al. [25]	2014	Uruguay	Retrospective single-centre	Patients with metastatic CUP-NET who underwent somatostatin receptor PET/CT for primary tumour localization	29	59.5 ± 10.6	12/17 (41%)	Liver (79%), lymph nodes (17%), lung (4%)	Well differentiated: 72%; moderately or poorly differentiated: 28%
Schreiter et al. [26]	2014	Germany	Retrospective single-centre	Patients with known/suspicious NET who underwent somatostatin receptor PET/CT for staging (including a subgroup of patients with metastatic CUP-NET)	33	56.3 (32–83)	13/20 (39%)	Liver (70%), lymph nodes (58%), bone (21%), lung (6%), other (9%)	Low grade: 49%; intermediate grade: 15%; high grade: 18%; unknown: 18%
Tan et al. [27]	2014	Malaysia	Retrospective single-centre	Patients with metastatic CUP-NET who underwent somatostatin receptor PET/CT for primary tumour localization	6	46 (28–56)	5/1 (83%)	Liver (100%)	Well differentiated: 100%
Naswa et al. [28]	2012	India	Prospective single-centre	Patients with metastatic CUP-NET who underwent somatostatin receptor PET/CT for primary tumour localization	20	55	10/10 (50%)	Liver (95%), bone (30%), lymph nodes (15%), other (10%)	NR
Łapińska et al. [29]	2011	Poland	Retrospective single-centre	Patients with known/suspicious NET who underwent somatostatin receptor PET/CT for staging (including a subgroup of patients with metastatic CUP-NET)	11	NR	NR	Liver and lung	NR
Prasad et al. [30]	2010	Germany and Italy	Prospective bi-centric	Patients with metastatic CUP-NET who underwent somatostatin receptor PET/CT for primary tumour localization	59	65 ± 9	33/36 (56%)	Liver (78%), lymph nodes (51%), bone (29%), lung (5%)	Well-differentiated: 76%; moderately differentiated: 3%; poorly differentiated or undifferentiated: 7%; unknown: 14%

CT = computed tomography; CUP-NET = neuroendocrine tumour with unknown primary; NR = not reported; PET = positron emission tomography; PRRT = peptide receptor radionuclide therapy

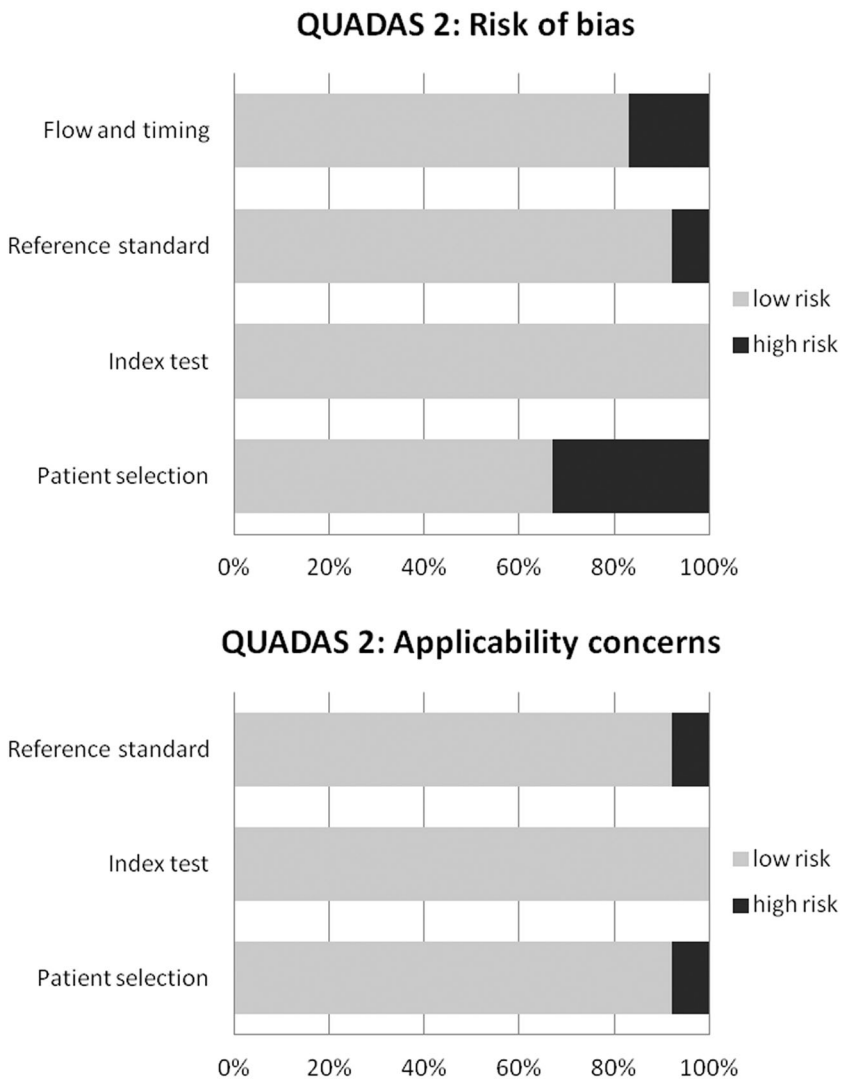

Fig. 2 Overall quality assessment of the studies included in the systematic review according to QUADAS-2 tool

In studies comparing somatostatin receptor PET/CT with conventional imaging, a clearly superior diagnostic performance of somatostatin receptor PET/CT in detecting CUP-NETs was demonstrated [21, 22, 25, 30]. Furthermore, somatostatin receptor PET/CT detected more CUP-NETs compared with somatostatin receptor scintigraphy [20, 22, 26]. The diagnostic performance of somatostatin receptor PET/CT seems to be influenced by the NET differentiation; in fact as NET differentiation lowered, radiolabelled somatostatin analogues uptake decreased in metastatic and primary NET lesions, whereas ^{18}F-FDG uptake showed a gradual rise [19]. Sampathirao et al. [19] found that the DR of CUP-NETs by using somatostatin receptor PET/CT was highest in G1, well-differentiated NETs (65.7%), and decreased as the proliferative index increased (37–50% in G2 and G3 NETs). Conversely the DR of CUP-NETs by using 18F-FDG PET/CT increased with intermediate- and high-grade NET.

Some articles evaluated the change of management obtained by using somatostatin receptor PET/CT for detecting CUP-NETs: this value ranged from 10 to 50% [25, 27, 28, 30].

Quantitative analysis (meta-analysis)

Twelve studies including 383 metastatic patients were selected for the meta-analysis on the DR of CUP-NET by somatostatin receptor PET/CT [19–30]. The DR of somatostatin receptor PET/CT in detecting CUP-NET in patients with metastatic disease on a per patient-based analysis ranged from 29 to 83%, with a pooled estimate of 56% (95% CI: 48–63%) (Fig. 3). The heterogeneity among the included studies was moderate ($I^2 = 50\%$). A publication bias was not detected by Egger's test ($p = 0.45$).

Performing a subgroup analysis taking into account the different type of study design, no significant difference of

Table 2 Technical aspects of somatostatin receptor PET/CT in the included studies

Authors	Radiotracer	Hybrid imaging modality	Radiotracer injected activity	Time interval between radiotracer injection and image acquisition	Image analysis	Reference standard	Comparison with other imaging methods
Sampathirao et al. [19]	^{68}Ga-DOTATATE	PET/CT with low-dose CT	NR	NR	Visual and semi-quantitative (SUV_{max})	Histology or further imaging	^{18}F-FDG PET/CT and conventional imaging
Menda et al. [20]	^{68}Ga-DOTATOC	PET/CT with low-dose CT	145–185 MBq	60 min	Visual	Histology, imaging or clinical follow-up	^{111}In-octreotide scintigraphy
Kazmierczak et al. [21]	^{68}Ga-DOTATATE	PET/CT with contrast-enhanced CT	206 ± 41 (127–302) MBq	60 min	Visual and semi-quantitative (SUV_{max} and tumour to spleen ratio)	Histology or further imaging	contrast-enhanced CT
Sadowski et al. [22]	^{68}Ga-DOTATATE	PET/CT with low-dose CT	185 MBq	60 min	Visual and semi-quantitative (SUV_{max})	Histology, imaging or clinical follow-up	^{111}In-octreotide SPECT/CT and conventional imaging
Pruthi et al. [23]	^{68}Ga-DOTANOC	PET/CT with contrast-enhanced CT	111–148 MBq	60 ± 15 min	Visual and semi-quantitative (SUV_{max})	Histology or further imaging	-
Nakamoto et al. [24]	^{68}Ga-DOTATOC	PET/CT with low-dose or contrast-enhanced CT	130 MBq	60 min	Visual and semi-quantitative (SUV_{max})	Histology or clinical follow-up	-
Alonso et al. [25]	^{68}Ga-DOTATATE	PET/CT with low-dose CT	104.2 ± 18.8 MBq	30 min	Visual and semi-quantitative (SUV_{max})	Histology, imaging or clinical follow-up	CT
Schreiter et al. [26]	^{68}Ga-DOTATOC	PET/CT with low-dose or contrast-enhanced CT	112.5 (66–200) MBq	60 min	Visual and semi-quantitative (SUV_{max})	Histology, imaging or clinical follow-up	^{111}In-octreotide SPECT/CT
Tan et al. [27]	^{68}Ga-DOTATATE	PET/CT with low-dose CT	160 (145–185) MBq	45–60 min	Visual and semi-quantitative (SUV_{max})	Histology, imaging or clinical follow-up	-
Naswa et al. [28]	^{68}Ga-DOTANOC	PET/CT with low-dose CT	132–222 MBq	45–60 min	Visual and semi-quantitative (SUV_{max})	Histology, imaging or biochemical follow-up	-
Łapińska et al. [29]	^{68}Ga-DOTATATE	PET/CT with low-dose CT	111–185 MBq	45–60 min	Visual and semi-quantitative (SUV_{max})	Histology when available	-
Prasad et al. [30]	^{68}Ga-DOTANOC	PET/CT with low-dose or contrast-enhanced CT	46–260	60–90 min	Visual and semi-quantitative (SUV_{max})	Histology, imaging or biochemical follow-up	CT

MBq = MegaBecquerel; NR = not reported; PET/CT = positron emission tomography/computed tomography; SPECT = single photon emission computed tomography; SUV_{max} = maximal standardized uptake value

Table 3 Main findings of the articles included in the meta-analysis

Authors	DR of CUP-NET by somatostatin receptor PET/CT (patient-based analysis)	Site of CUP-NET detected by somatostatin receptor PET/CT (lesion-based analysis)					Change of management obtained by using somatostatin receptor PET/CT
		Pancreas	Bowel	Lung	Stomach	Other	
Sampathirao et al. [19]	31/51 (61%)	10/31 (32%)	17/31 (55%)	2/31 (6%)	1/31 (3%)	1/31 (3%)	NR
Menda et al. [20]	15/40 (38%)	6/15 (40%)	8/15 (53%)	0/15 (0%)	0/15 (0%)	1/15 (7%)	NR
Kazmierczak et al. [21]	30/38 (79%)	12/34 (35%)	19/34 (56%)	2/34 (6%)	0/34 (0%)	1/34 (3%)	NR
Sadowski et al. [22]	4/14 (29%)	NR	NR	NR	NR	NR	NR
Pruthi et al. [23]	40/68 (59%)	7/41 (17%)	27/41 (66%)	1/41 (2%)	4/41 (10%)	2/41 (5%)	NR
Nakamoto et al. [24]	7/14 (50%)	1/7 (14%)	6/7 (86%)	0/7 (0%)	0/7 (0%)	0 (0%)	NR
Alonso et al. [25]	17/29 (59%)	7/17 (41%)	9/17 (53%)	0/17 (0%)	1/17 (6%)	0/17 (0%)	7/29 (24%)
Schreiter et al. [26]	15/33 (45%)	NR	NR	NR	NR	NR	NR
Tan et al. [27]	5/6 (83%)	4/5 (80%)	0/5 (0%)	0/5 (0%)	1/5 (20%)	0/5 (0%)	3/6 (50%)
Naswa et al. [28]	12/20 (60%)	1/12 (8%)	9/12 (75%)	1/12 (8%)	1/12 (8%)	0/12 (0%)	3/20 (15%)
Łapińska et al. [29]	5/11 (45%)	1/5 (20%)	3/5 (60%)	0/5 (0%)	0/5 (0%)	1/5 (20%)	NR
Prasad et al. [30]	35/59 (59%)	16/35 (46%)	16/35 (46%)	2/35 (6%)	0/35 (0%)	1/35 (3%)	6/59 (10%)
Pooled results	56% (95% CI: 48–63)						20% (95% CI: 10–33)

CUP-NET = unknown primary neuroendocrine tumour; DR = detection rate; NR = not reported

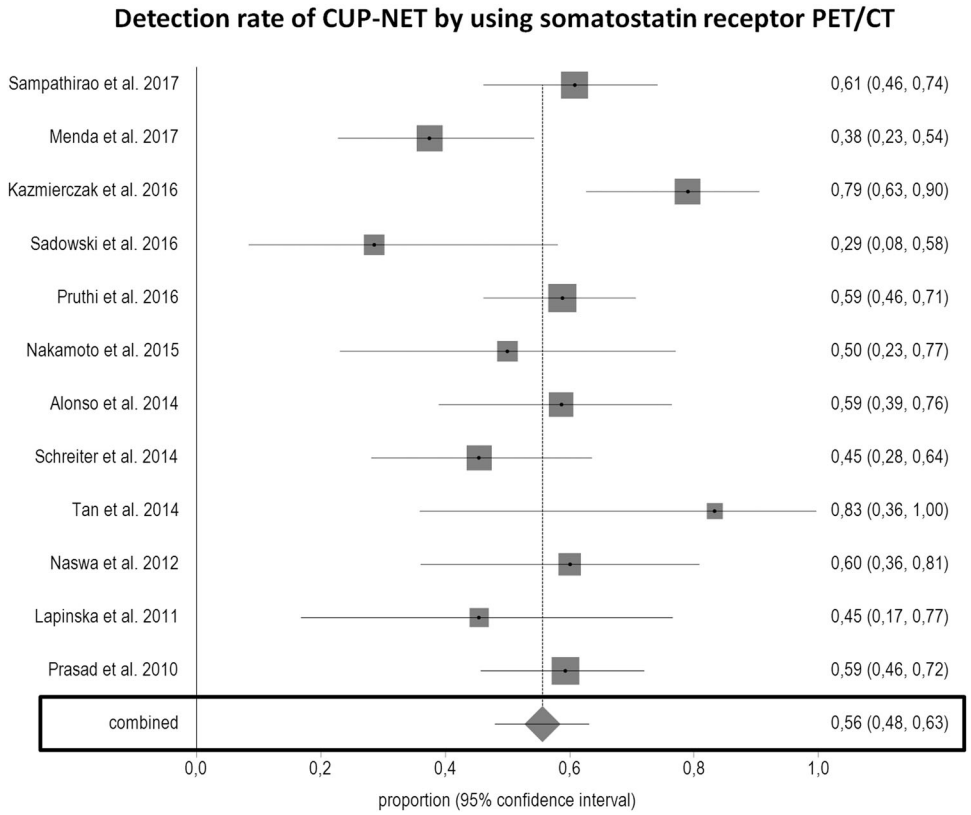

Fig. 3 Plots of individual studies and pooled detection rate of somatostatin receptor PET/CT in patients with CUP-NET on a per patient-based analysis, including 95% confidence intervals (95% CI). The size of the squares indicates the weight of each study

DR of CUP-NET by using somatostatin receptor PET/CT was found between prospective studies (pooled DR = 48%; 95% CI: 34–62%) and retrospective studies (pooled DR = 60%; 95% CI: 51–68%).

Subgroup analyses taking into account the type of radiotracer demonstrated a trend toward a higher pooled DR of CUP-NET by using ^{68}Ga-DOTATATE (60%; 95% CI: 45–73%) or ^{68}Ga-DOTANOC (59%; 95% CI: 51–67%) compared with ^{68}Ga-DOTATOC PET/CT (43%; 95% CI: 33–53%), without a statistical significant difference.

Four studies including 114 patients were selected for the meta-analysis on the percentage of change of management by using somatostatin receptor PET/CT in CUP-NETs [25, 27, 28, 30]. The pooled percentage of change of management by using somatostatin receptor PET/CT was 20% (95% CI: 9–33%) (Fig. 4). The heterogeneity among the included studies was moderate ($I^2 = 50\%$). A publication bias was not detected by Egger's test ($p = 0.07$).

Discussion

To the best of our knowledge, this is the first meta-analysis evaluating the DR and the change of management by using somatostatin receptor PET/CT in patients with CUP-NETs.

Several studies have used somatostatin receptor PET/CT in detecting CUP-NETs reporting different values of DR. However, most of these studies have limited power, owing to the relatively small numbers of patients enrolled and assessed. In order to derive more robust estimates on the DR of somatostatin receptor PET/CT in this setting we have pooled the published studies. A systematic review process was adopted in ascertaining studies and the quality of the included studies was assessed by using the QUADAS-2 tool [16]. Furthermore, a random-effects model taking into account the variability between studies was used for the quantitative analysis [15].

Several studies addressed the need to identify the primary site in metastatic CUP-NETs since the therapeutic management may change depending on the site of origin of NETs [36]. There is evidence that an effort should be made to localize the CUP-NET even in the presence of metastatic disease because resection of the primary tumour(s) may improve disease-free and overall survival, and because the choice of chemotherapeutic agent depends on the location of the primary tumour [12]. However, it has been underlined that the search for CUP-NET must be weighed against the need to initiate prompt treatment [37].

Both European NeuroEndocrine Tumor Society (ENETS) and National Comprehensive Cancer Network guidelines recommend that additional imaging tools, including somatostatin receptor PET/CT, should be exploited to identify a

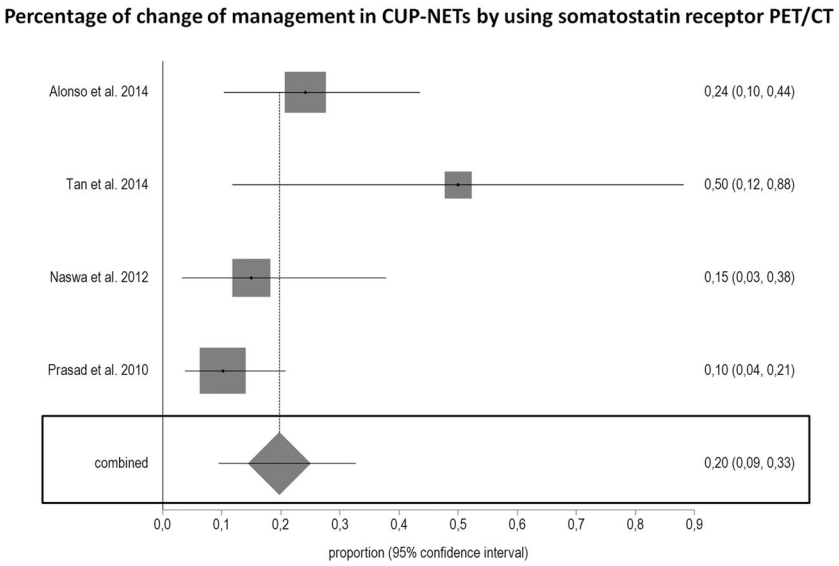

Fig. 4 Plots of individual studies and pooled percentage of change of management by using somatostatin receptor PET/CT in patients with CUP-NET on a per patient-based analysis, including 95% confidence intervals (95% CI). The size of the squares indicates the weight of each study

CUP-NET [36, 38]. If the primary tumour remains unknown, therapeutic decision making is essentially based on grading, functionality, somatostatin receptor status, tumour extent, and hepatic tumour burden [36, 38].

Findings of our systematic review and meta-analysis indicate that the use of somatostatin receptor PET/CT may reduce the number of unidentified CUP-NETs, leading to a change of management in a significant percentage of patients. The most-frequent sites of CUP-NET detected by somatostatin receptor PET/CT were bowel and pancreas; this finding is not surprising as these are the most frequent locations of primary NETs [2].

However, in some cases, CUP-NETs may not be identified even if a thorough diagnostic work-up including somatostatin receptor PET/CT is employed. Causes of false-negative findings at somatostatin receptor PET/CT may be owing to small lesions or with low SSTR expressions or with cystic component (i.e., some pancreatic NETs) or located near or in sites of physiological radiotracer uptake [4, 11].

Available literature data demonstrate that somatostatin receptor PET/CT detected more CUP-NETs compared with somatostatin receptor scintigraphy [20, 22, 26]; this is not surprising owing to the higher diagnostic performance of somatostatin receptor PET/CT compared with somatostatin receptor scintigraphy in NETs [4, 12].

Both somatostatin receptor PET/CT and fluorine-18 dihydroxyphenylalanine (^{18}F-FDOPA) PET/CT could be used as hybrid imaging methods for detection of CUP-NET in patients with well-differentiated NETs [4]. Unfortunately, to date there are not studies comparing somatostatin receptor PET/CT and fluorine-18 dihydroxyphenylalanine (^{18}F-FDOPA) PET/CT for detecting CUP-NETs. ^{18}F-FDOPA uptake in NETs is related to the ability of these tumours to take up and decarboxylate amine precursors [4, 39]. ^{18}F-FDOPA PET/CT appears to be a sensitive functional imaging tool for the detection of CUP-NETs not visualized by somatostatin receptor scintigraphy, especially tumours with a well-differentiated pattern and serotonin secretion [40]. ^{18}F-FDOPA PET/CT appears to be useful for detection of well-differentiated NETs of the small bowel, in particular, multifocal NETs of the ileum. For detecting pancreatic NETs, the high background uptake of ^{18}F-FDOPA by the normal exocrine pancreas can be somewhat overcome by pretreatment with carbidopa [12]. Overall, both somatostatin receptor PET/CT and ^{18}F-FDOPA PET/CT may be performed for the detection of midgut NETs, whereas somatostatin receptor PET/CT appears to be a better first-line nuclear imaging modality for pancreatic NETs [12].

^{18}F-FDG PET/CT may be an additional diagnostic test for suspicious poorly differentiated CUP-NETs and for prognostication [4]. In fact, when NET differentiation is reduced, radiolabelled somatostatin analogues uptake usually decreases and ^{18}F-FDG uptake usually rises [19].

Heterogeneity among studies may represent a potential source of bias in a meta-analysis. This heterogeneity is likely to arise through baseline differences among the patients in the included studies (Table 1), diversity in methodological aspects between different studies (Table 2), and different study quality. We detected a moderate heterogeneity among the studies in our pooled analysis ($I^2 = 50\%$) and we tried to explain this heterogeneity performing subgroup analyses based on different study design or radiopharmaceutical injected. Statistical significant differences of DR of somatostatin receptor PET/CT based on the different study design (prospective versus retrospective) or the type or radiotracer (^{68}Ga-DOTATATE, ^{68}Ga-DOTANOC, or ^{68}Ga-DOTATOC) were not found in our subgroup analyses.

Publication bias is a major concern in all meta-analyses as studies reporting significant positive findings are more likely to be published than those reporting negative results. Indeed, it is not unusual for small-sized early studies to report positive findings that subsequent larger studies fail to replicate. We did not find a significant publication bias in our meta-analysis about the calculation of DR of somatostatin receptor PET/CT and about the percentage of change of management obtained with this imaging method.

Diagnostic accuracy of a test is not a measure of clinical effectiveness and improved accuracy does not necessarily result in improved patient outcomes. Overall, our systematic review and meta-analysis demonstrated that somatostatin receptor PET/CT may reduce the number of CUP-NETs that remain unidentified changing the management in a significant number of patients.

Large multicentric prospective studies and cost-effectiveness analyses are needed to strengthen the usefulness of this technique in this setting. In particular, more prospective studies on the change of management by using somatostatin receptor PET/CT in patients with CUP-NET are warranted.

Conclusions

Somatostatin receptor PET/CT is a very useful imaging method in detecting CUP-NETs in patients with metastatic disease. More studies on the change of management by using this imaging method in this setting are needed.

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Compliance with ethical standards

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

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