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META-ANALYSIS

Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis

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Abstract Gallium-68 somatostatin receptor (SMSR) positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) are valuable diagnostic tools for patients with neuroendocrine tumours (NETs). To date, a meta-analysis about the diagnostic accuracy of these imaging methods is lacking. Aim of our study is to meta-analyse published data about the diagnostic performance of SMSR PET or PET/CT in patients with thoracic and/or gastroenteropancreatic (GEP) NETs. A comprehensive computer literature search of studies published in PubMed/MEDLINE, Scopus and Embase databases through October 2011 and regarding SMSR PET or PET/CT in patients with NETs was carried out. Only studies in which SMSR PET or PET/CT were performed in patients with thoracic and/or GEP NETs were selected (medullary thyroid tumours and neural crest derived tumours were excluded from the analysis). Pooled sensitivity, pooled specificity and area under the ROC curve were calculated to measure the diagnostic accuracy of SMSR PET and PET/CT in NETs. Results: Sixteen studies comprising 567 patients were included in this meta-analysis. The pooled sensitivity and specificity of SMSR PET or PET/CT in detecting NETs were 93% (95% confidence interval [95% CI]: 91–95%) and 91% (95% CI: 82–97%), respectively, on a per patient-based analysis. The area under the ROC curve was 0.96. In patients with suspicious thoracic and/or GEP NETs, SMSR PET and PET/CT demonstrated high sensitivity and specificity. These accurate techniques should be considered as first-line diagnostic imaging methods in patients with suspicious thoracic and/or GEP NETs.

Keywords PET · PET/CT · Somatostatin analogues · Neuroendocrine tumours · Gallium-68

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Introduction

Epidemiological data show a worldwide increase in the prevalence and incidence of thoracic and gastroenteropancreatic (GEP) neuroendocrine tumours (NETs) in the past few decades, which is probably due to improved methods of detection of these tumours [1, 2]. The diagnosis of NETs usually represents a challenge for the clinicians because their small size and variable anatomic location limit their detection using conventional imaging procedures such as computed tomography (CT), ultrasonography (US), and magnetic resonance imaging (MRI). Furthermore, NETs detection could be missed by fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) due to the common slow metabolic rate of these tumours [3–5].

NETs overexpress somatostatin receptors (SMSRs) on their cell surface and this represents the rationale for the use of somatostatin analogues for diagnosis and therapy of these tumours; in fact, SMSR imaging noninvasively provides data on receptor expression on NETs cells with direct therapeutic implications [3–5].

Somatostatin receptor scintigraphy (SRS), usually performed using Indium-111 DTPA-octreotide, is still considered as the gold standard for staging of NETs [6, 7]. However, several clinical studies have clearly demonstrated

the superiority of Gallium-68 somatostatin receptor positron emission tomography/computed tomography (SMSR PET/CT) over SRS [3]. Furthermore, a recent study demonstrated that SMSR PET/CT is considerably cheaper than SRS [8]. Currently, the use of SMSR PET/CT is limited to specialised centres as part of clinical trials [3, 4]. Nevertheless, it could be hypothesised that SMSR PET/CT will substitute SRS in the clinical practice for the diagnosis of NETs in the near future.

Several studies showed that SMSR PET and PET/CT, using different radiopharmaceuticals (as Gallium-68 DOTANOC, Gallium-68 DOTATOC and Gallium-68 DOTATATE) are accurate imaging methods in the diagnosis of thoracic (mainly pulmonary and thymic) and GEP NETs; nevertheless, a meta-analysis on this topic is still lacking in the literature. Therefore, the purpose of this study is to meta-analyse published data on the diagnostic performance of SMSR PET and PET/CT in patients with thoracic and/or GEP NETs, in order to add evidence-based data in this setting.

Methods

Search strategy

A comprehensive computer literature search of the PubMed/MEDLINE, Scopus and Embase databases was carried out to find relevant published articles on the diagnostic performance of SMSR PET or PET/CT in patients with thoracic and/or GEP NETs. We used a search algorithm that was based on a combination of the terms: (a) ''PET'' OR "positron emission tomography" and (b) "neuroendocrine" OR "NET". No beginning date limit was used; the search was updated until 31 October 2011 and no language-based restriction was used. To expand our search, references of the retrieved articles were also screened for additional studies.

Study selection

Studies or subsets in studies investigating the diagnostic performance of SMSR PET or PET/CT in patients with thoracic and/or GEP NETs were eligible for inclusion.

Only those studies or subsets in studies that satisfied all of the following criteria were included: (a) SMSR PET or PET/CT performed in patients with thoracic and/or GEP NETs; (b) sample size of at least 8 patients with NET.

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 (sample size of less than 8 patients with NET); (d) articles including only patients with medullary thyroid carcinoma and/or paragangliomas and/or other neural crest derived tumours; (e) insufficient data to reassess sensitivity (number of true positive and false negative) and specificity (number of true negative and false positive) on a per patient-based analysis from individual studies; (f) duplicate data (in such cases the most complete article was included in the meta-analysis).

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

Data abstraction

For each included study, information was collected concerning basic study (author names, journal, year of publication, country of origin), patient characteristics (mean age, sex, number of patients performing SMSR PET or PET/CT, number and types of NETs investigated), technical parameters (device and radiopharmaceutical used, radiopharmaceutical injected dose, time interval between radiopharmaceutical injection and image acquisition, acquisition protocol, image analysis and reference standard used). For each study the number of true positive, false positive, true negative and false negative findings for SMSR PET or PET/CT in thoracic and/or GEP NETs were recorded. Patients with medullary thyroid carcinoma, paragangliomas and other neural crest derived tumours were excluded from the analysis.

Quality assessment

The methodological quality of the included studies was assessed by using Quality Assessment of Diagnostic Accuracy Studies criteria.

Statistical analyses

Sensitivity and specificity of SMSR PET or PET/CT were calculated on a per patient-based analysis. The sensitivity was determined from the number of true positive and false negative results obtained from individual studies; the specificity was calculated from the number of true negative and false positive results obtained from individual studies. We used a random effect model for statistical pooling of the data. Pooled data are presented with 95% confidence intervals (95% CI). A I-square statistic was performed to test for heterogeneity between studies. The area under the ROC curve was calculated to measure the accuracy of SMSR PET or PET/CT in patients with thoracic and/or

GEP NETs. Statistical analyses were performed using Meta-DiSc statistical software version 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain) [9].

Results

Literature search

The comprehensive computer literature search from the PubMed/MEDLINE, Scopus and Embase databases revealed 1822 articles. Reviewing titles and abstracts, 1774 articles were excluded: 1664 because they were not in the field of interest of this review, 94 as reviews or editorials, 16 as case reports or small case series.

Forty-eight articles were selected and retrieved in full-text version; no additional study was found screening the references of these articles. From these 48 articles potentially eligible for inclusion, after reviewing the full-text article, 27 studies were excluded because sensitivity and specificity of SMSR PET or PET/CT could not be calculated on a per patient-based analysis for insufficient data; moreover, 5 articles were excluded for data overlap. Finally, 16 studies, comprising a total sample size of 567 patients with NETs met all inclusion criteria, and they were included in this meta-analysis [10–25] (Fig. 1). The characteristics of the included studies are presented in Tables 1 and 2.

Quality assessment

Overall, the methodological quality of the included studies was medium–high.

Diagnostic performance

The diagnostic performance results of SMSR PET or PET/CT in the 16 included studies are presented in Table 3. Sensitivity and specificity of SMSR PET or PET/CT on a per patient-based analysis ranged from 72 to 100% and from 67 to 100%, with pooled estimates of 93% (95% CI: 91–95%) and 91% (95% CI: 82–97%), respectively (Figs. 2, 3). The included studies were statistically heterogeneous in their estimates of sensitivity (I-square: 66%) and specificity (I-square: 61%). The area under the ROC curve was 0.96, demonstrating that SMSR PET or PET/CT are accurate diagnostic methods in NETs diagnosis (Fig. 4).

A meta-regression analysis correlating the diagnostic accuracy of SMSR PET or PET/CT to the site and kind of NETs was not performed. In fact, in many articles there was a mixture of thoracic and GEP NETs (Table 1) and NETs with various degrees of differentiation; therefore, separate analysis was not possible. Nevertheless, it can be reasonably argued that SMSR PET or PET/CT seem to be accurate methods both in thoracic than in GEP NET, especially in patients with well-differentiated NETs. Due to

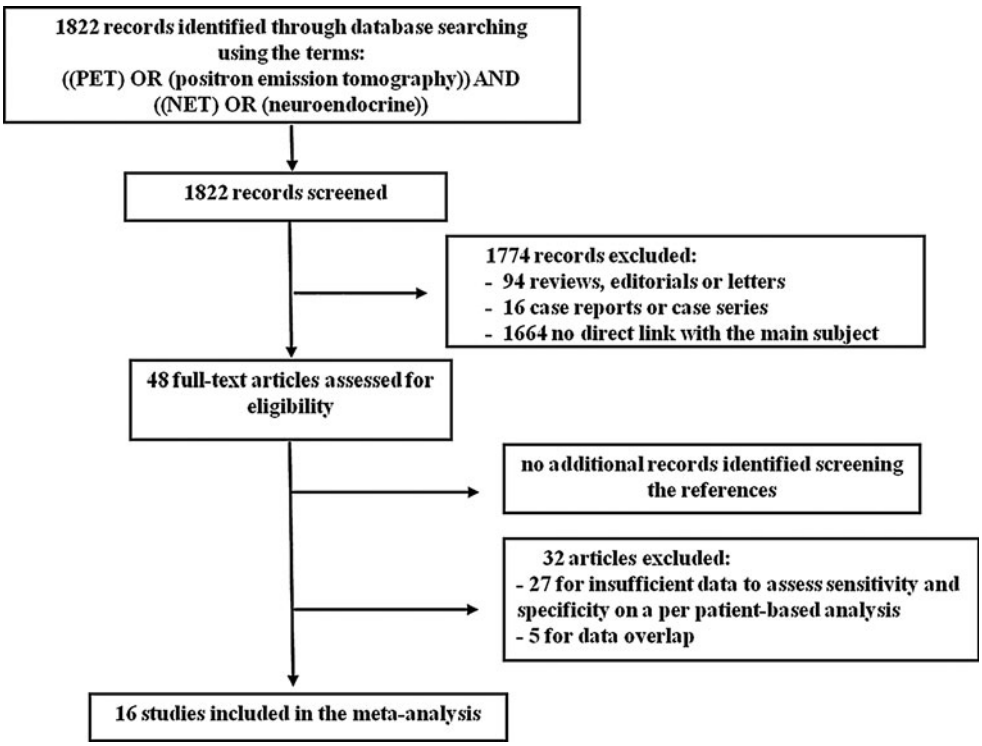

Fig. 1 Flow chart of the search for eligible studies on the diagnostic performance of somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours

Table 1 Basic study and patient characteristics

Authors	Year	Country	Patients performing SMSR PET or PET/CT	Mean age (years)	%Male	Type of neuroendocrine tumours evaluated
Hofmann et al. [10]	2001	Germany	8	60	75	6 GEP, 2 lung
Koukouraki et al. [11]	2006	Germany	22	52	64	9 GEP, 4 CUP, 2 lung, 2 thymus, 5 other
Gabriel et al. [12]	2007	Austria	84	58	57	50 GEP, 9 CUP, 6 lung, 19 other
Buchmann et al. [13]	2007	Germany	27	52	48	15 GEP, 8 CUP, 1 lung, 3 other
Kayani et al. [14]	2008	UK	38	53	66	28 GEP, 4 CUP, 6 lung
Ambrosini et al. [15]	2008	Italy	13	63	54	11 GEP, 2 lung
Ambrosini et al. [16]	2009	Italy	11	62	55	11 lung
Kayani et al. [17]	2009	UK	18	56	44	18 lung
Haug et al. [18]	2009	Germany	25	57	64	14 GEP, 6 lung, 4 CUP, 1 other
Frilling et al. [19]	2010	Germany	52	52	48	49 GEP, 1 CUP, 2 lung
Jindal et al. [20]	2010	India	20	33	55	20 lung
Krausz et al. [21]	2010	Israel	19	60	63	15 GEP, 2 CUP, 1 lung, 1 other
Srirajaskanthan et al. [22]	2010	UK	51	55	53	37 GEP, 6 CUP, 2 lung, 2 thymus, 4 other
Versari et al. [23]	2010	Italy	19	56	58	13 GEP, 6 other
Ruf et al. [24]	2011	Germany	51	57	49	33 GEP, 4 lung, 14 other
Naswa et al. [25]	2011	India	109	50	53	109 GEP

SMSR PET Gallium-68 somatostatin receptor PET, *GEP* gastroenteropancreatic, *CUP* carcinoma with unknown primary

the small number of studies performing SMSR PET alone (Table 2), a comparison of PET/CT versus PET alone was not possible.

Discussion

SMSR imaging represents an important topic in NETs diagnosis [3, 26–28]. Evidence-based data from our analysis suggest that SMSR PET and PET/CT are accurate methods in the diagnosis of thoracic and GEP NETs. Several single-centre studies using SMSR PET or PET/CT have reported high sensitivity and specificity of these techniques in patients with NETs (Table 3). However, many of these studies have limited power, analyzing only relatively small numbers of patients. To derive more robust estimates of diagnostic performance of SMSR PET and PET/CT we pooled published studies. A systematic review process was adopted in ascertaining studies; we have attempted to avoid selection bias by including all relevant studies and adopting rigid inclusion criteria in our analysis.

Pooled results of our analysis indicate that SMSR PET and PET/CT demonstrate high sensitivity (93%; 95% CI: 91–95%) and high specificity (91%; 95% CI: 82–97%) to detect thoracic and GEP NETs. Furthermore, the area under the ROC curve value (0.96) demonstrates that SMSR PET and PET/CT are accurate methods for the diagnosis of thoracic and GEP NETs.

Nevertheless, possible causes of false positive and false negative results of these imaging methods should be kept in mind. False negative results could be related to small lesions or NETs with a low expression of SMSR (for example undifferentiated NETs). On the other hand, false positive results could be related to other diseases; in particular, inflammatory diseases may cause false positive results because activated inflammatory cells may overexpress SMSR.

Heterogeneity between studies may represent a potential source of bias; the included studies were statistically heterogeneous in their estimates of sensitivity and specificity. Since systematic reviews bring together studies that are different both clinically and methodologically, heterogeneity in their results is to be expected. For example, heterogeneity is likely to arise through diversity in technical aspects (Table 2), study quality and inclusion criteria.

Publication bias is a major concern in all forms of pooled analyses, as studies reporting significant findings are more likely to be published than those reporting non-significant results. Indeed, it is not unusual for small-sized early studies to report a positive relationship that subsequent larger studies fail to replicate. We cannot exclude a publication bias in our analysis, but we tried to minimise it

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

Authors	Device	Radiopharmaceutical used	Injected activity	Time between tracer injection and image acquisition	Acquisition protocol	Image analysis	Reference standard
Hofmann et al. [10]	PET	^{68}Ga-DOTATOC	80–250 MBq	Immediately	Dynamic + static images	Visual and semiquantitative	Morphological imaging
Koukouraki et al. [11]	PET	^{68}Ga-DOTATOC	150–230 MBq	Immediately	Dynamic + static images	Visual, semiquantitative and quantitative	Histology and/or morphological imaging
Gabriel M et al. [12]	PET	^{68}Ga-DOTATOC	NR	100 min	Static images	Visual	Histology and/or clinical/imaging follow-up
Buchmann et al. [13]	PET	^{68}Ga-DOTATOC	100–228 MBq	45 min	Static images	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Kayani et al. [14]	PET/CT	^{68}Ga-DOTATATE	120–200 MBq	45–60 min	Static images	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Ambrosini et al. [15]	PET/CT	^{68}Ga-DOTANOC	185 MBq	60 min	Static images	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Ambrosini et al. [16]	PET/CT	^{68}Ga-DOTANOC	185 MBq	60–90 min	Static images	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Kayani et al. [17]	PET/CT	^{68}Ga-DOTATATE	120–200 MBq	45–60 min	Static images	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Haug et al. [18]	PET/CT	^{68}Ga-DOTATATE	200 MBq	60 min	Static images	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Frilling et al. [19]	PET/CT	^{68}Ga-DOTATOC	120–250 MBq	60 min	Static images	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Jindal et al. [20]	PET/CT	^{68}Ga-DOTATOC	74–111 MBq	45–60 min	Static images	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Krausz et al. [21]	PET/CT	^{68}Ga-DOTANOC	83–184 MBq	56–96 min	Static images	Visual and semiquantitative	Histology and/or clinical/imaging follow-up
Srirajaskanthan et al. [22]	PET/CT	^{68}Ga-DOTATATE	120–200 MBq	60 min	Static images	Visual	Histology and/or clinical/imaging follow-up
Versari et al. [23]	PET/CT	^{68}Ga-DOTATOC	1.5–2 MBq/Kg	60 min	Static images	Visual	Histology and/or clinical/imaging follow-up
Ruf et al. [24]	PET/CT	^{68}Ga-DOTATOC	100–120 MBq	60 min	Static images	Visual	Histology and/or clinical/imaging follow-up
Naswa et al. [25]	PET/CT	^{68}Ga-DOTANOC	132–222 MBq	45–60 min	Static images	Visual and semiquantitative	Histology and/or clinical/imaging follow-up

selecting only articles that included at least 8 patients with thoracic or GEP NETs.

In our meta-analysis, we chose to calculate pooled sensitivity and specificity on a per patient-based analysis (instead of a per lesion-based or a per region-based analysis) because most of the Authors have adopted this criterion. However, we cannot exclude the potential bias derived from this choice, but there were not sufficient data to obtain significant results performing a per region- or a per lesion-based pooled analysis. Furthermore, it was not possible to perform a sub-analysis comparing PET versus PET/CT results because there were only four studies performing PET alone as reported in Table 2.

SMSR PET and PET/CT were performed in the included studies using three different radiopharmaceuticals (Gallium-

Table 3 Diagnostic performance of somatostatin receptor PET or PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours on a per patient-based analysis

Authors	No. of patients included	True positive	False positive	True negative	False negative	Sensitivity (95% CI)	Specificity (95% CI)
Hofmann et al. [10]	8	8	0	0	0	100% (63–100)	NC
Koukouraki et al. [11]	22	21	0	0	1	95% (77–100)	NC
Gabriel et al. [12]	84	69	1	12	2	97% (90–100)	92% (64–100)
Buchmann et al. [13]	27	27	0	0	0	100% (87–100)	NC
Kayani et al. [14]	38	31	0	0	7	82% (66–92)	NC
Ambrosini et al. [15]	11[a]	11	0	0	0	100% (72–100)	NC
Ambrosini et al. [16]	11	9	0	2	0	100% (66–100)	100% (16–100)
Kayani et al. [17]	18	13	0	0	5	72% (47–90)	NC
Haug et al. [18]	25	24	0	0	1	96% (80–100)	NC
Frilling et al. [19]	52	52	0	0	0	100% (93–100)	NC
Jindal et al. [20]	20	19	0	0	1	95% (75–100)	NC
Krausz et al. [21]	19	19	0	0	0	100% (82–100)	NC
Srirajaskanthan et al. [22]	51	41	0	4	6	87% (74–95)	100% (40–100)
Versari et al. [23]	19	12	1	5	1	92% (64–100)	83% (36–100)
Ruf et al. [24]	51	32	4	8	7	82% (66–92)	67% (35–90)
Naswa et al. [25]	109	75	0	32	2	97% (91–100)	100% (89–100)

NC not calculable, *NR* not reported

[a] Two patients with pulmonary neuroendocrine tumours cited in a subsequent publication were excluded from the analysis

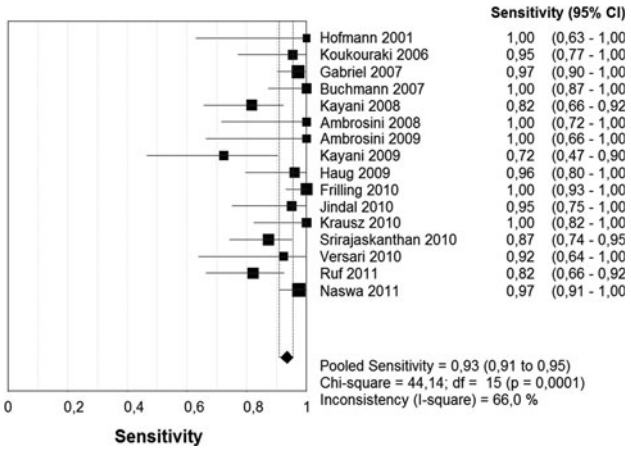

Fig. 2 Plot of individual studies and pooled sensitivity of somatostatin receptor PET and PET/CT in thoracic and gastroenteropancreatic neuroendocrine tumours including 95% confidence intervals. The size of the *squares* indicates the weight of each study

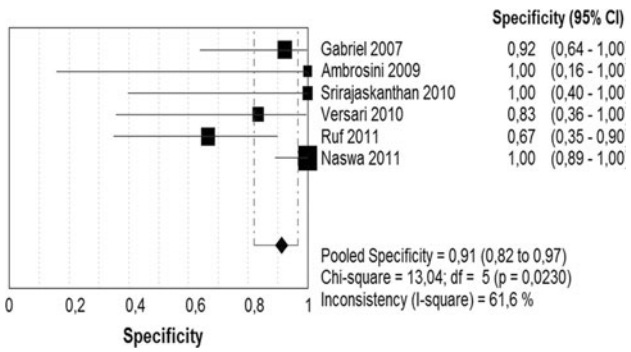

Fig. 3 Plot of individual studies and pooled specificity of somatostatin receptor PET and PET/CT in thoracic and gastroenteropancreatic neuroendocrine tumours including 95% confidence intervals. The size of the *squares* indicates the weight of each study

68 DOTATOC, Gallium-68 DOTATATE and Gallium-68 DOTANOC) (Table 2) which differ about the binding profile for the five somatostatin receptor subtypes (sst1–5): whereas Gallium-68 DOTATATE is selective for sst2, Gallium-68 DOTATOC binds to sst2 with high affinity and to sst5 with reasonable affinity; finally, Gallium-68 DOTANOC has high affinity to sst2, sst3, and sst5 [3]. We cannot exclude the potential bias derived from pooling the data obtained by using different radiopharmaceuticals; nevertheless, the differences in SMSR-binding affinities mentioned above have not yet found a direct clinical correlate [3]; some preliminary experiences have demonstrated a difference in NETs detection using the various somatostatin analogues on a per lesion-based analysis [29, 30], but a difference on a per patient-based analysis has not yet been demonstrated.

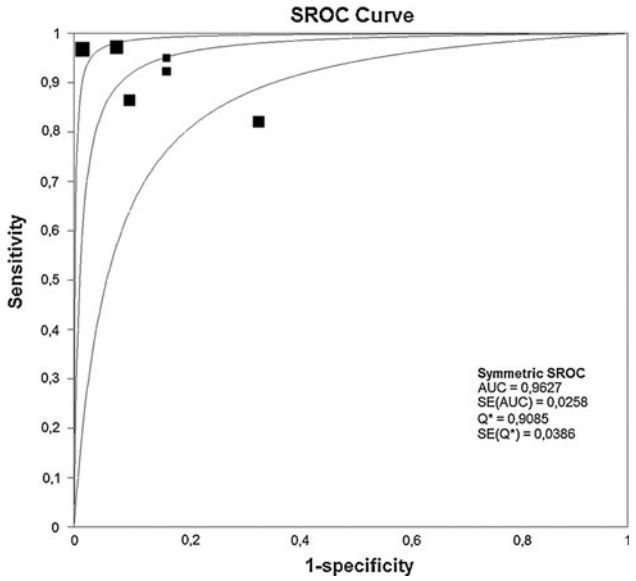

Fig. 4 Summary ROC curve of diagnostic accuracy of Gallium-68 somatostatin receptor PET and PET/CT in thoracic and gastroenteropancreatic neuroendocrine tumours

Conclusions

In patients with suspected thoracic and/or GEP NETs, SMSR PET and PET/CT demonstrated high sensitivity and specificity. Nevertheless, possible causes of false negative and false positive results should be kept in mind when interpreting the SMSR PET and PET/CT findings. These accurate techniques should be considered as first-line diagnostic imaging methods in patients with suspicious thoracic and/or GEP NETs; however, large multicenter studies are necessary to substantiate the high diagnostic accuracy of SMSR PET and PET/CT in this setting.

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