

The Diagnostic Performance of 68Ga-PET or PET/CT in Neuroendocrine Tumour, A Meta Analysis

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Abstract

Objective: To evaluate the diagnostic performance of 68Ga-PET or PET/CT in neuroendocrine tumour (NET) with a meta-analysis.

Methods: The major electronic medical databases, PubMed, The cochrance Library, Embase.com, Web of Science, were searched for relevant papers up to February 2018. According to the inclusion and exclusion criteria, the eligible literature was graded with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS). Pooled sensitivity specificity Diagnostic odds ratio DOR and Summary Receiver Operating Characteristics (SROC) and the areas under the curve AUC were calculated with Meta-Disc 1.4 software. The publication bias was assessed with Stata 12.0 software.

Results: A total of 14 studies were finally included. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio of 68Ga-PET or PET/CT were 90.4% (95% CI, 87.5%-92.8%), 84.2% (95% CI, 79.3%-88.3%), 4.646 (95% CI, 3.222-6.699), 0.135 (95% CI, 0.095-0.192) and 41.082 (95% CI, 23.114-73.018), respectively. The AUC and Q* indexes of the SROC were 0.9319 and 0.8674, respectively. Deek's funnel plot shows symmetry (P=0.48), and Begg's and Egger's test results indicating that there was no publication bias.

Conclusion: This meta-analysis suggested that 68Ga-PET or PET/CT have higher sensitivity and specificity by detecting primary and metastatic lesions to diagnose neuroendocrine tumour.

Keywords: 68Ga; PET; Diagnosis; Neuroendocrine tumour; Meta-analysis

Introduction

Neuroendocrine tumors (NETs) is a kind of mainly distributed in the lung, gastrointestinal tract and pancreas organs, and it is rare and slow-growing tumours. Some studies have shown that the incidence of NETs is increasing year by year, it depends on the diagnostic technology advances and the gradual improvement of the people understanding of disease [1]. The correct staging and grading for the NETs by clinicians can lead to a five-year survival rate of about 75%. After early detection, surgical treatment can be performed. In fact, it often loses the best chance of surgical resection for NETs [1]. Therefore, it is very important to accurately diagnose and provide appropriate treatment for the disease in the early stage. Due to various factors, such as tumour size, location of lesions and metabolism, traditional imaging methods, such as CT, ultrasound and magnetic resonance imaging, have low detection rate for NETs. With the development of medical technology, the 68Ga labelling of somatostatin receptor in nuclear medical imaging technology has led to the gradual application of PET in the diagnosis, treatment and management of neuroendocrine tumours [2]. At present, 68Ga-DOTA-TATE, 68Ga-DOTA-TOC and 68Ga-DOTA-NOC are the most widely used clinical researches [2]. However, due to differences in geographical indications, indications and sample size, the conclusion of published research has inconsistent in evaluating the value of 68Ga-PET imaging. Therefore, this meta-analysis is used to analyse the diagnostic value of 68Ga-PET or PET/CT imaging in neuroendocrine tumours.

Materials and Methods

Inclusion and Exclusion Criteria

Inclusion criteria: (1) The literature used 68ga-pet or PET/CT

imaging diagnosis NETs. (2) The subjects were diagnosed as NETs by pathology or clinical follow-up. (3) The literature data can calculate four-fold table data, this is true positive (TP), false positive (FP), false negative (FN) and true negative (TN). (4) The literature was analyzed by studying the number of patients not lesions.

Exclusion criteria: (1) Review, conference papers, case reports and repeated studies. (2) Unable to access full text.

Literature search

The English literature published were researched by two evaluators in database of PubMed, The cochrance Library, Embase.com, and Web of Science form the establishment of the database to February 2018. At the same time, it also tracks the references of newly published system evaluation or meta analysis. Researching words: (1) "68Ga OR Ga68 OR Ga-68 OR Ga OR gallium" and (2) "PET" OR "positron emission tomography" OR "positron emission tomography/computed tomography" OR "PET/CT" OR "positron emission tomography-computed tomography" OR "PET-CT" and (3) "Neuroendocrine tumors" OR "NETs".

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Literature selection and data extraction

The retrieved literature was imported into the document manager Endnote X7 to remove duplicate references. Two evaluators independently select the literatures according to the prior setting inclusion and exclusion criteria, and finally determine the qualified studies. If the opinion is not consistent, through negotiation or third party discussion. The basic characteristics of included study are as follows: Gender, age, author, published year, country, type of study (prospective or retrospective), diagnostic criteria for disease, sample size, blind method, type of imaging agent (68Ga-DOTA-TATE, 68Ga-DOTA-TOC or 68Ga-DOTA-NOC).

Literature quality evaluation

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) [3], recommended by the Cochrane collaborative network was used to assess the Quality of the included studies. Deletion nonobligatory items of 3, 8 and 9 items and determine ultimately the evaluation criteria 11 items. Each item is evaluated with "yes", "no" or "not clear".

Statistical analysis

Meta-analysis was performed using meta-disc 1.4 software [4]. The threshold effect was tested by ROC curve and Spearman correlation coefficient. If threshold effect exists, the best way to pool data is to fit the Summary Receiver Operating Characteristics (SROC) curve and calculate areas under the curve (AUC). If no threshold effect, we will calculate the combined sensitivity (Sen), specificity (Spe), Positive likelihood thewire (LR+) and Negative likelihood thewire (LR-) and Diagnostic odds ratio (DOR). Meanwhile, meta-regression analysis was used to find the heterogeneity source. Deek's funnel plot analysis was conducted with Stata 12.0 software to detect publish bias (Table 1).

Results

Included literature

A total of 752 literatures were retrieved, the title and abstract were reviewed, and 108 were left out of the literatures that were significantly unrelated to the subject and repeated. After careful reading, the reasons for the exclusion of 90 articles were: (1) 32 of 90 were excluded because of review, case report, editor's letter and animal experiment 32; (2) 18 articles were unable to extract the complete four table data, the literatures only reported the sensitivity and no specificity data; (3) 40 articles only evaluated 68 Ga-PET or PET/CT for the management of disease staging and not evaluated diagnosis performance. Finally, 14 papers were included.

The basic features of the included literature

There were seven studies of prospective [5-11] and retrospective [12-18], respectively. Three articles [5,7,11] imaging instruments were PET, and 11 were PET/CT [6-8], [10-12], [12-18]. Eight [6-9,10,13-17] articles study methods were blinded and another six articles [5,7,8,11,12,18] not given. Eight studies [5,7-10,15-17] photographic developer were 68Ga-DOTATOC and four studies [11,12,14,18] were 68Ga-DOTATATE and two studies [6,13] were 68Ga-DOTANOC.

The quality evaluation of the included literature

This study used the QUADAS tool to evaluate the quality. Six articles had nine questions answered "yes", another two questions answered "no or unclear". Eight articles had eight questions answered "yes", another three questions answered "no or unclear".

Author	Year	Device	design type	age	imaging agent	68Ga dose	blind	golden standard	QUADAS	
									yes	No or unclear
Gabriel et al	2007	PET	Prospective	58.2	68Ga-DOTATOC	100-150 MBq	NG	histopathology, imaging, follow-up	9	2
Buchmann et al	2007	PET	Prospective	52	68Ga-DOTATOC	100-228 MBq	NG	histopathology	8	3
Versari et al	2010	PET-CT	Retrospective	56	68Ga-DOTATOC	1.5-2 MBq/Kg	yes	fine needle biopsy and/or surgery	9	2
Ruf et al	2011	PET-CT	Retrospective	57	68Ga-DOTATOC	100-120 MBq	yes	clinical and imaging follow-up, histopathology	9	2
Naswa et al	2011	PET/CT	Prospective	50	68Ga-DOTANOC	132-222 MBq	yes	histopathology	9	2
Lapińska et al	2011	PET/CT	Retrospective	54	68Ga-DOTATATE	111-185 MBq	NG	histopathology	8	3
Mayerhoefer et al	2012	PET-CT	Retrospective	61.9	69Ga-DOTATOC	150 MBq	yes	histopathology, imaging examinations	8	3
Haug et al	2012	PET/CT	Retrospective	58	68Ga-DOTATATE	200 MBq	NG	histopathology or clinical follow-up	8	3
Beiderwellen et al	2013	PET-CT	Prospective	54	68Ga-DOTATOC	51±11MBq	NG	histopathology	9	2
Schraml et al	2013	PET-CT	Prospective	57	68Ga-DOTATOC	150 MBq	yes	histopathology	8	3
Venkitaraman et al	2014	PET-CT	Prospective	34.22	68Ga-DOTATOC	74-111 MBq	yes	histopathology	9	2
Srirajaskanth et al	2010	PET	prospective	55.5	68Ga-DOTATATE	120-200 MBq	NG	histopathology	8	3
Naswa et al	2014	PET/CT	Retrospective	48.8	68Ga-DOTANOC	132-222 MBq	yes	histopathology	8	3
Haug et al	2014	PET/CT	Retrospective	58	68Ga-DOTATATE	200 MBq	yes	histopathology	8	3

NG: not given, QUADAS: Quality Assessment of Diagnostic Accuracy Studies.

Table1: Basic study and patient characteristics.

The results of meta-analysis

According to the result of SROC curve plane scatter diagram and Spearman correlation coefficient is 0.152, there were no threshold effect. (P=0.604). Further to analyze the other sources of method heterogeneity. We have calculated the heterogeneity of Sen, Spe, LR+, LR and DOR and the heterogeneity of sensitivity indicated that there was a slight heterogeneity between the studies (I²=56.1%, P=0.0054). Therefore, meta regression was conducted to explore the heterogeneity sources, and the main analysis of variables related to the study (such as research type, research design, blind method, imaging instruments and photographic developer, etc.). The results showed that the heterogeneity of this study was related to the blind method of the study design, namely, the accuracy of the blind method was 3.89 higher than that of the non-blind method [RDOR=3.89 (95%CI,1.05-14.44), P=0.047].

Summery statistic

Because of mild heterogeneity, the random effects model was used to quantitative combined weighted the result of Sen 90.4% (95% CI, 87.5%-92.8%), Spe 84.2% (95% CI, 79.3%-88.3%), LR+ 4.646 (95% CI, 3.222-6.699), LR- 0.135 (95% CI, 0.095-0.192) and DOR 41.082 (95% CI, 23-114 73.018), respectively (Figures 1-3). According to the SROC, the AUC and Q* indexes of curves are 0.9319 and 0.8674, respectively (Figure 4).

Publication bias

The Deek 'funnel plot drawn by Stata 12.0 software shows the basic symmetry of the graph, indicating that there is no publication bias (P=0.48) (Figure 5).

Discussions

The uniqueness of neuroendocrine tumor is the overexpression of somatostatin receptor in tumor cells, which provides a reliable basis for

imaging diagnosis and peptide receptor nuclide therapy [2]. Octreotide marked In-111 is the first recognized somatostatin receptor to be used to diagnose neuroendocrine tumors, which was approved for release In the United States in June 1994 [19]. Although the Octreotide of imaging agent successfully used to diagnose NETs more than 20 years, but it needed relatively high gamma ray energy to complete imaging (171 kev-245 kev), and need use the medium energy probe to scan, and its image spatial resolution is low. At the end of 1990 there were 68Ga- DOTA imaging agent were applied to clinical, the tumor cells in one hour after the rapid uptake can quickly complete PET imaging after injection in patients, and improve the image quality and spatial resolution [2]. This study collected publicly published literature on the 68Ga PET or PET/CT and evaluated its diagnostic accuracy in NETs using a meta-analysis.

In this study, the results of meta-analysis were carried out and indicated that the 68Ga PET or PET/CT had higher accuracy in diagnosis of NETs, with a pooled sensitivity and specificity of 90.4% and 84.2%, respectively. In addition, the DOR is 41.082 and the AUC and Q* indices of SROC is 0.9319 and 0.8674, and further indicated that the 68Ga PET or PET/CT had higher accuracy in NETs.

Some researchers [20], analyzed the application value of 68Ga-DOTATOC PET imaging in NETs with meta-analysis. They analyzed the photographic developer of 68Ga-DOTATOC in diagnosing and changing clinical management decisions for NETs, and the sensitivity and specificity were 92% (95% CI, 85%-96%), 82% (95% CI,69%-90%), respectively. However, the heterogeneity of the inclusion literature were not analyzed in their study. Treglia et al. [21] analyzed also the diagnostic efficacy of 68Ga PET or PET/CT in NETs. Their study had included 16 literatures, but only 5 literatures could extract the complete four table data. The sensitivity and specificity of the combination were 93% (95% CI: 91-95%) and 91% (95% CI: 82-97%), respectively. The heterogeneity was too high in their study, although the meta-regression analysis failed to find the source of heterogeneity.

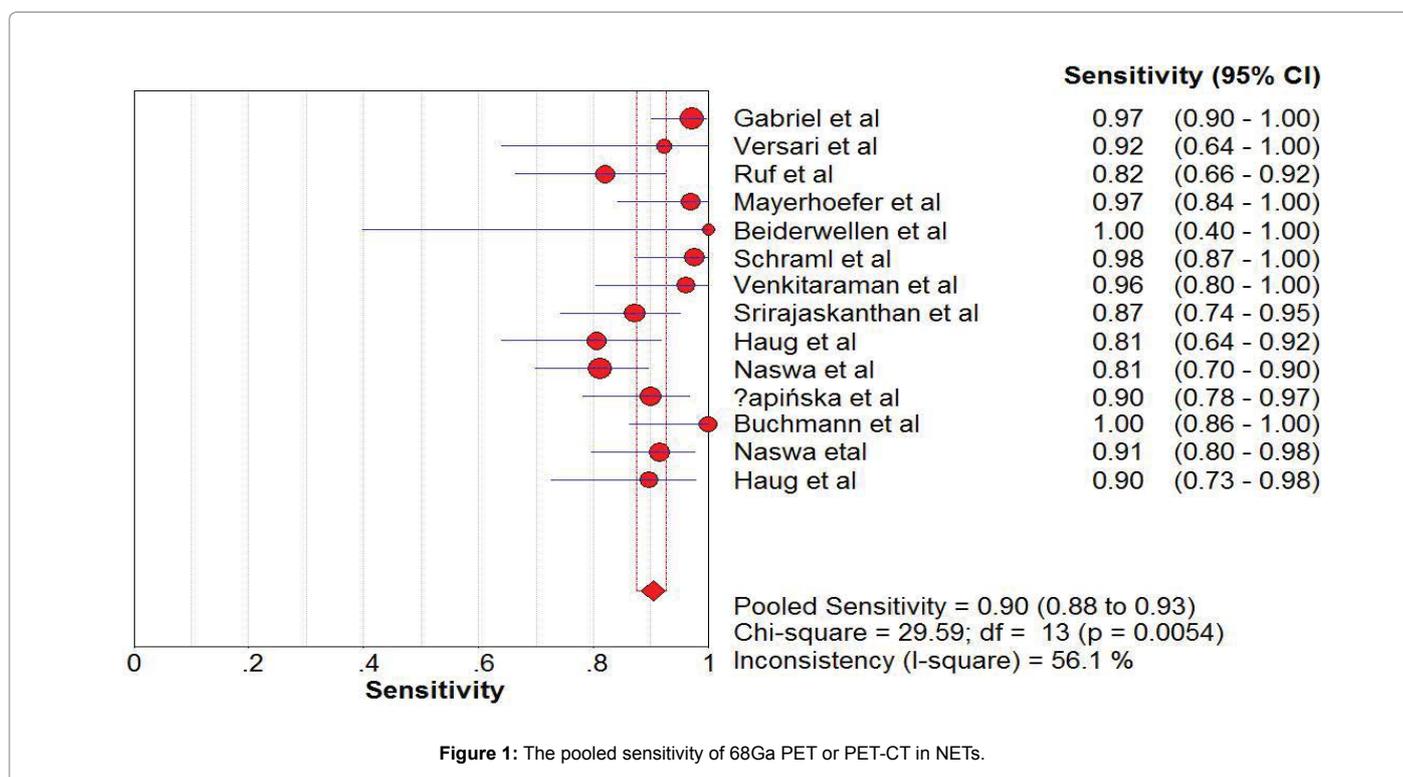


Figure 1: The pooled sensitivity of 68Ga PET or PET-CT in NETs.

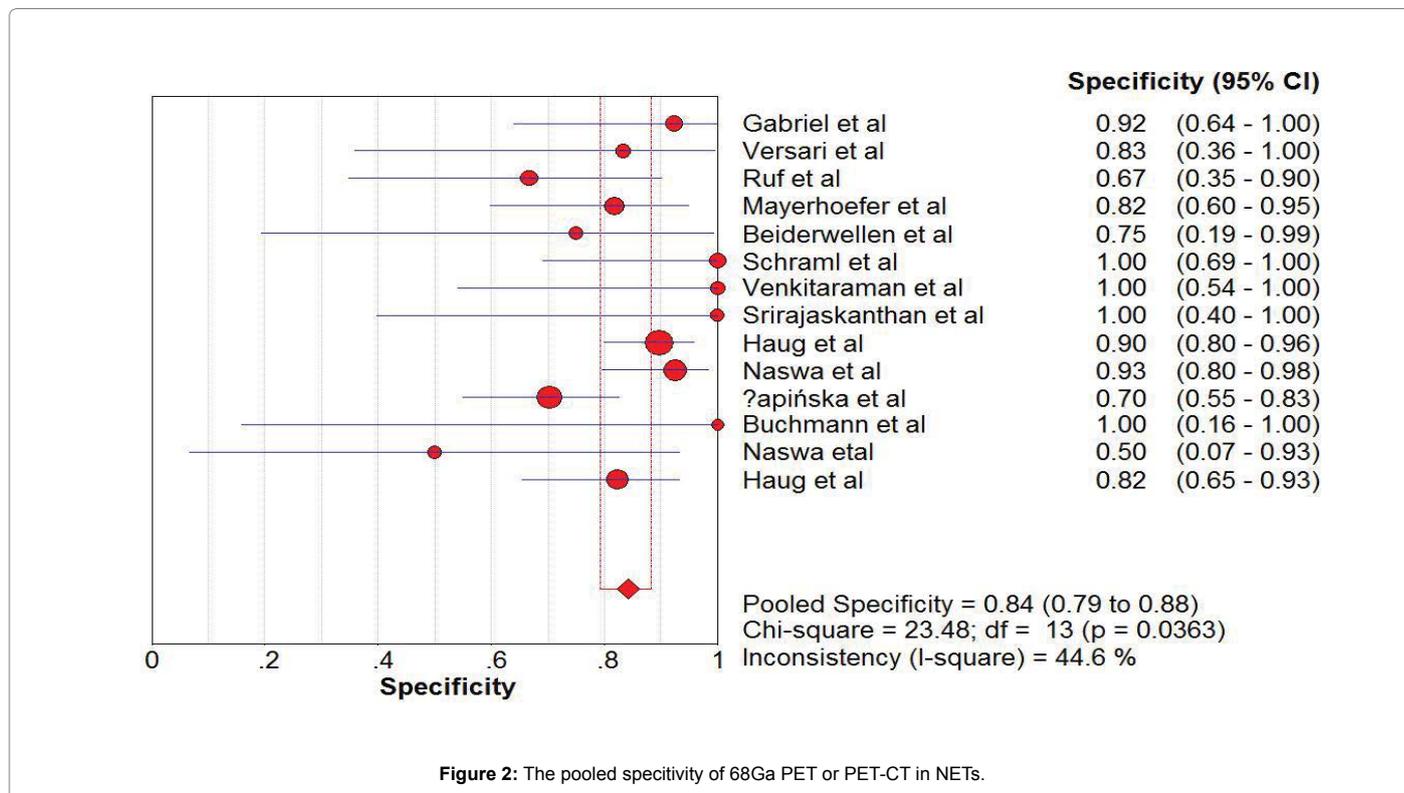


Figure 2: The pooled specificity of 68Ga PET or PET-CT in NETs.

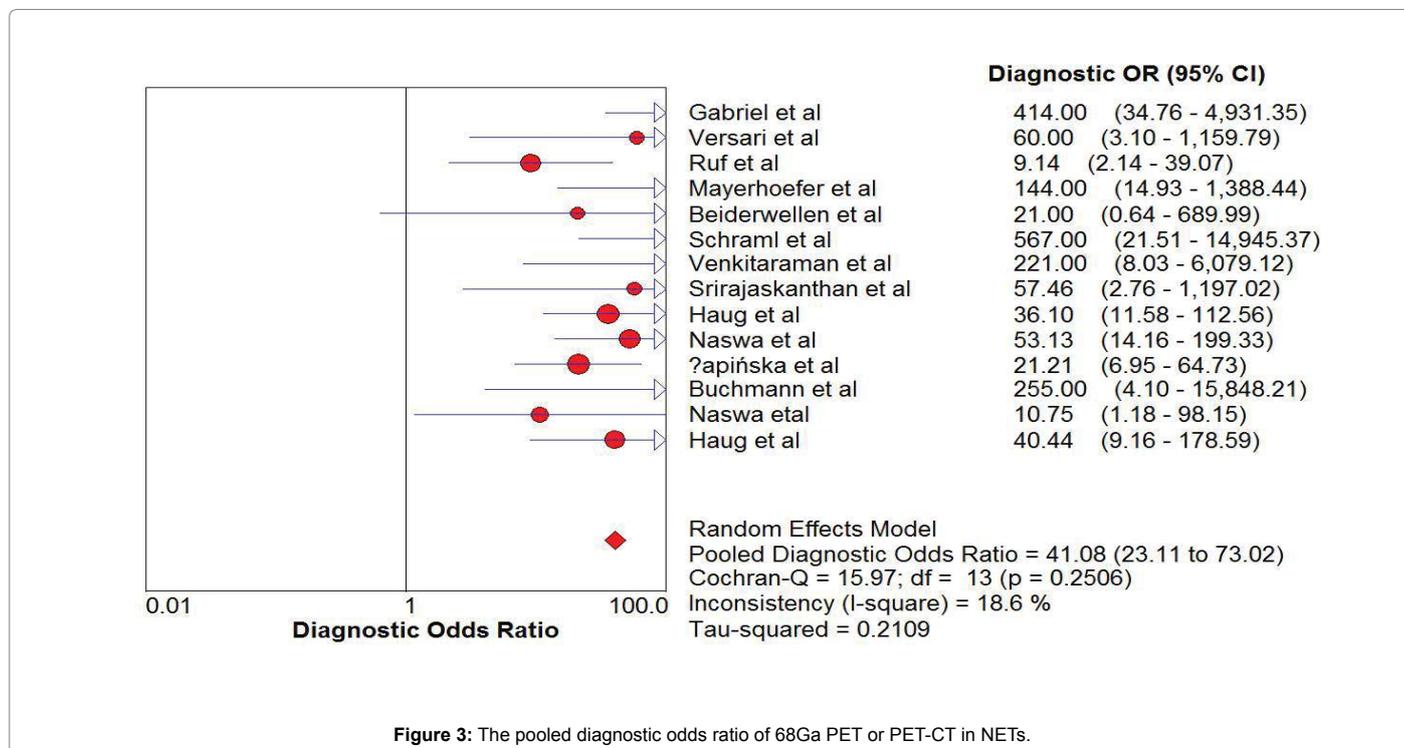


Figure 3: The pooled diagnostic odds ratio of 68Ga PET or PET-CT in NETs.

In our study, the pooled sensitivity and specificity were 90.4% and 84.2%, roughly the same as other results. It is well to be reminded that our study have included three imaging agents of 68Ga-DOTATOC, 68Ga-DOTATATE and 68Ga-DOTANOC and each article can extract the complete four table data, and this study discussed the heterogeneity test and heterogeneity source.

To discuss the source heterogeneity is an important part of meta analysis. The results of our study indicated that there are slight heterogeneity in this meta analysis. It is important that we found the blind is the source of heterogeneity, and the accuracy of the blind method was 3.89 times higher than that non-blind method. Publication

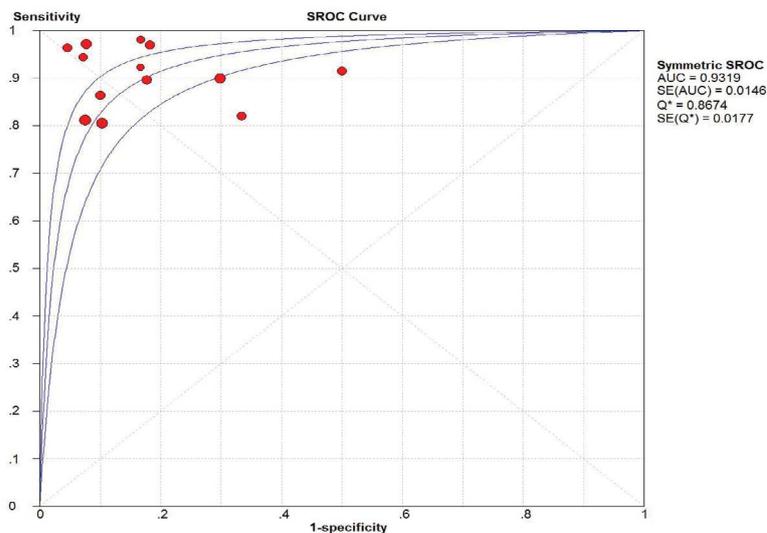


Figure 4: The SROC curve of 68Ga PET or PET-CT in NETs.

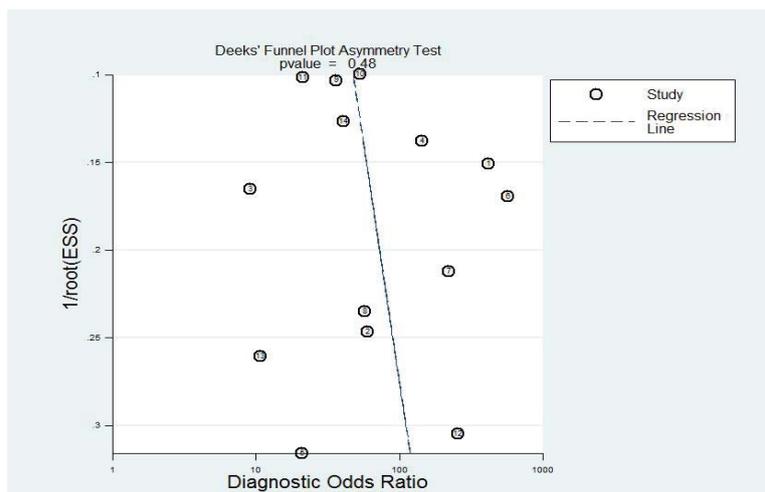


Figure 5: The funnel plot of Deek'testqq.

bias is another important factor in the reliability of meta analysis results. In this paper, Deek's funnel plot results indicated that there is no publication bias, which further indicates that our results of this study are more reliable.

Conclusion

This meta-analysis suggested that 68Ga-PET or PET/CT have higher sensitivity and specificity by detecting primary and metastatic lesions to diagnose neuroendocrine tumour.

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