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Evidence Summary PET 18

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

PET Imaging in Paraneoplastic Neurological Syndromes

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Table of Contents

PET Imaging in Paraneoplastic Neurological Syndromes

Evidence Summary

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

INTRODUCTION

Paraneoplastic neurological syndromes (PNS) are a rare group of nervous system disorders associated with the presence of an occult malignancy but not caused by a direct effect of the primary tumour or its metastases [1]. The majority of these disorders are likely immune-mediated, either by antibody- or T-cell-related mechanisms [2]. Antibodies can be generated in response to a tumour antigen, termed onconeural antibodies, which also cross-react with a target in the nervous system. PNS can affect various components of the central and peripheral nervous systems, including the neuromuscular junction. Certain antibodies are associated with particular PNS, and also with specific underlying malignancies [3]. In many cases, the presentation of PNS precedes the clinical manifestation of the malignancy itself. Treatment of PNS varies depending on the syndrome, and may include immunosuppression, treatment of the underlying tumour, or both. Early diagnosis of the underlying malignancy is therefore vital to achieving optimal treatment and better outcome for the patients.

Given the rarity of the condition, diagnosis of PNS requires a high degree of clinical suspicion. The initial stage of the investigation involves testing for onconeural antibodies in serum and CSF and, depending on the clinical presentation, brain magnetic resonance imaging (MRI) and electrophysiology. If well-characterized onconeural antibodies are detected or if a classic PNS is suspected, image-based screening for an underlying tumour can be performed. Conventional imaging such as computerized tomography (CT), ultrasound (US), and mammogram are commonly used modalities; however, these techniques have limitations in detecting occult malignancies as they are based on structural changes and usually focus on limited parts of the body. Functional imaging with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) or PET/CT may be able to detect tumours associated with PNS otherwise missed by conventional imaging.

In Ontario, access to PET scans is regulated by a provincial PET Steering Committee. PET scan requests that do not fall under standard protocol are referred to the PET Access program to be reviewed by a panel of experts for approval. As PET scans are a costly and limited resource, current practice when investigating PNS is to utilize conventional imaging as initial investigation, and only proceed to a PET scan if these tests are inconclusive. For that reason, the aim of the present review is to provide a summary of evidence demonstrating the value of PET or PET/CT in detecting the underlying tumour in patients with PNS.

RESEARCH QUESTION

What is the diagnostic accuracy of PET or PET/CT in detecting occult malignancies in patients with PNS?

TARGET POPULATION

Patients suspected of PNS, with positive or negative onconeural antibodies, who had negative conventional imaging prior to PET scan.

INTENDED USERS

This evidence summary is intended to guide the Ontario PET Steering Committee in their decision making with respect to the development of indications. This evidence summary may also be useful to inform clinicians who are involved in the management of patients with PNS.

METHODS

This evidence summary was developed by a Working Group consisting of a neuro-oncology fellow (CH) and a health research methodologist (RP) at the request of the Ontario PET Steering Committee.

The Working Group was responsible for reviewing the identified evidence and drafting the summary. Conflict of interest declarations for all authors are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. Published systematic reviews or systematic reviews as part of practice guidelines were considered eligible for inclusion. The search was aimed at finding a review that covered the research question and could be used, at least in part, as the evidentiary basis for this evidence summary. The electronic databases MEDLINE (1946 to September 2016) and EMBASE (1974 to 2016 week 39) were searched through OVID. See Appendix 2 for the search strategy.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) [4] tool to determine whether existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

If no eligible systematic reviews were identified, a primary search of the literature was conducted and described below.

Literature Search Strategy

The primary literature was searched using MEDLINE (1946 to September 2016) and EMBASE (1974 to 2016 week 39) databases through OVID. Details of the literature search can be found in Appendix 2. In addition, reference lists from relevant systematic reviews and primary literature were scanned for potentially useful studies.

Study Selection Criteria and Process

Inclusion Criteria

1. Published as a full article in a peer-reviewed journal.
2. Evaluated the use of PET or PET/CT with ^{18}F-FDG
3. Post-biopsy or post-mortem histology, or clinical or radiologic follow-up were used as the reference standard for final diagnosis.

4. Patients had been investigated previously with conventional imaging (CT, US, MRI, mammography, where appropriate), which failed to identify an underlying malignancy.

Exclusion Criteria

1. Case reports, conference abstracts, literature or narrative reviews, letters, editorials, historical articles, or commentaries.
2. Insufficient information to calculate the number of true positive, false positive, false negative, and true negative results from the article.
3. Reports published in a language other than English.

A review of the titles and abstracts that resulted from the search was conducted independently by one reviewer, as were the items that warranted full-text review.

Data Extraction and Assessment of Study Quality and Potential for Bias

One reviewer extracted data from the included studies. For each article, the principal author, country of origin, publication year, study design, number of patients, age and sex, the type of PET and conventional imaging performed as well as the numeric data on diagnostic performance were recorded. All extracted data and information were audited by an independent auditor. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [5] was used to evaluate the risk of bias and applicability concerns for each eligible study.

Synthesizing the Evidence

Data were summarized in evidence tables and described in the text. When clinically homogenous results from two or more studies and sufficient data were available to reassess sensitivity and specificity of PET or PET/CT, a random effects model was used to produce summary estimates with 95% confidence intervals (CIs). The I^2 percentage was calculated as a measure of heterogeneity. Statistical analysis was undertaken using the software Meta-DiSc version 1.4, which implements meta-regression using a generalization of the Littenberg and Moses linear model [6,7].

RESULTS

Search for Existing Systematic Reviews

A search for systematic reviews did not yield an appropriate source document on which to build an evidence base. As such, the AMSTAR tool was not used.

Search for Primary Literature

Literature Search Results

A search for primary literature was conducted and a total of 139 unique citations were identified from the electronic searches, of which 126 were excluded after a review of titles and abstracts. Thirteen citations were considered as candidates, but upon full-text review, 11 did not meet the inclusion criteria. Finally, the remaining two studies were included in this systematic review. See Appendix 3 for the modified PRISMA flow diagram.

Study Design and Quality

Both studies were observational in nature; one study used a prospective design [8] while the other retrospectively reviewed the case records of patients [9]. Hadjivassiliou et al. [8] performed PET imaging using a modified gamma camera equipped with a low-dose CT system for anatomical localization and attenuation correction. Rees et al. [9] used a stand-alone PET

scanner. The duration of follow-up was noted in Rees et al. [9] and ranged from two to 44 months (mean, 18.1 months; median, 16 months). Hadjivassiliou et al. [8] did not specify the timing or length of follow-up. Details of the study characteristics can be found in Table 1. The risk of bias for each study was assessed according to the four QUADAS-2 domains (Appendix 4). There were no concerns regarding applicability; however, both studies were assessed as having a high risk of bias for flow and timing. In particular, a definite diagnosis of malignancy was not made in all cases as some patients died without histologic confirmation. This may have been a study limitation as obtaining a histological diagnosis from all patients is impractical. Furthermore, both studies lacked information about whether the interpretation of pathology results and extended follow-up were blinded to PET findings. According to the GRADE criteria, the results were consistent across both studies but suffer from imprecision due to low patient numbers. Taken as a whole, the quality of the evidence was judged to be moderate.

Table 1. Studies selected for inclusion.

Study, year	Country	Type of study	No. of patients	Median age	Gender (M/F)	PET imaging	CIM
Hadjivassiliou et al. 2009 [8]	UK	Prospective	80	NA	NA	PET/CT	CT
Rees et al. 2001 [9]	UK	Retrospective	43	62	24/19	PET	CT, US, mammo-graphy

Abbreviations: CIM, conventional imaging; CT, computed tomography; M/F, male/female; NA, not available; PET, positron emission tomography; UK, United Kingdom; US, ultrasound

Onconeural Antibodies

Serological testing for onconeural antibodies was performed in 91.9% (113/123) of patients from the two studies [8,9]. Ten patients had anti-Hu antibodies, two patients had voltage-gated calcium antibodies, one patient had anti-Yo antibodies, 38 patients were antibody-negative, and 62 patients had unspecified antibody status. Of the 34 patients with a positive PET or PET/CT scan, 10 patients had positive onconeural antibodies while 22 patients were negative (2 patients were not tested).

Diagnostic Accuracy

For the diagnosis of malignancy in patients clinically suspected of having PNS, a total of 114 patients from the combined cohort were included in the meta-analysis [8,9]. Nine patients were excluded from the analysis because their findings on PET or PET/CT could not be confirmed. The prevalence of malignancy was 12.0% (9/75) in the Hadjivassiliou et al. [8] study and 25.6% (10/39) in the Rees et al. [9] study. Of the total 19 patients with a proven malignancy, PET or PET/CT was positive in 17 patients (7 small cell lung cancer, 4 colon cancer, 2 non-small cell lung cancer, 1 non-Hodgkin lymphoma, 1 thymoma, 1 endometrial cancer, and 1 unknown primary) and negative in two patients (1 small cell lung cancer, 1 breast cancer). The pooled sensitivity and specificity on a per-patient based analysis were 89% (95% CI, 67% to 99%) and 92% (95% CI, 84% to 96%), respectively. The forest plots (**Figure 1 and 2**) showed no significant heterogeneity between the studies (I^2=0%).

Figure 1: Sensitivity of PET or PET/CT in detecting malignancy.

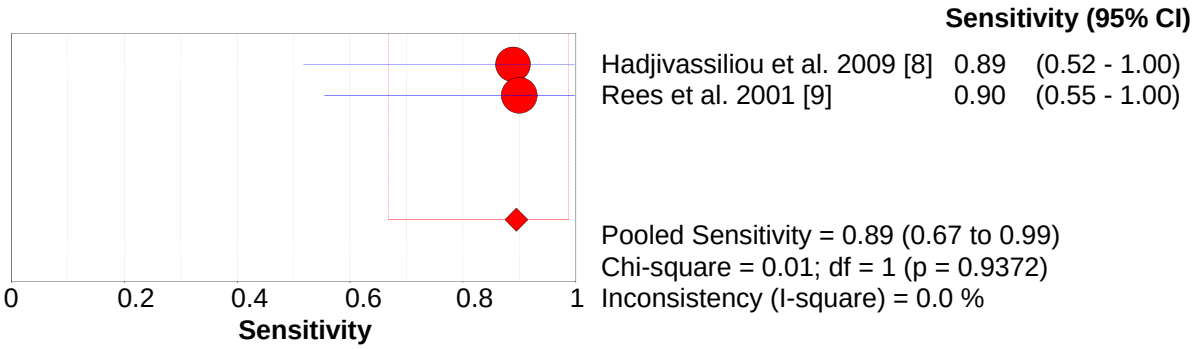
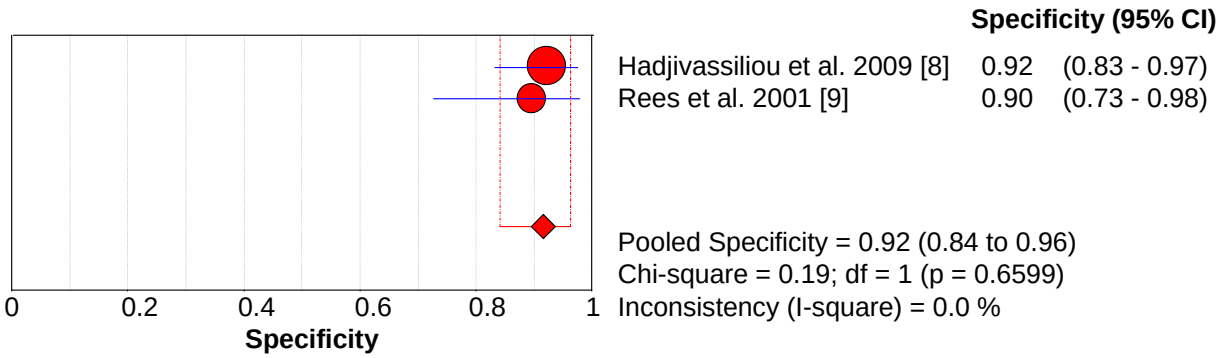


Figure 2: Specificity of PET or PET/CT in detecting malignancy.



DISCUSSION

Identification of an underlying malignancy is a crucial component in the management of PNS. The optimal diagnostic algorithm is unclear. Our current search of the literature attempts to determine the accuracy of PET scanning when added to the malignant work-up of patients with suspected PNS. Only two studies examining the usefulness of PET scans in patients with suspected PNS and negative conventional imaging were identified. The number of patients was limited, with 114 patients included in the meta-analysis. Given the rarity of PNS, this was not unexpected. Obtaining a larger sample size would require multiple, likely multinational centres with a longer follow-up period, which would pose significant challenges. A small sample size is likely an unavoidable limitation to these studies.

The overall detection rate of PET scanning was low at 17%. Considering the importance of detecting an underlying malignancy, this result can be interpreted as clinically significant. Furthermore, the pooled sensitivity was 89% and the pooled specificity was 92%. There was remarkable consistency between the sensitivity and specificity of both studies. These findings suggest that in patients suspected of having PNS but with negative conventional imaging, PET scan is likely to correctly identify those with an underlying malignancy. Nonetheless, there is the potential for false-positive scans as FDG is not a cancer-specific agent. In such cases,

further endoscopic procedures and biopsies are performed before considering treatment. Additionally, false-positive PET scans may provide clinically relevant information on non-malignant conditions that could explain the symptoms. Likewise, if no underlying malignancy is present, a negative PET scan will likely be correct in ruling out the disease. Based on this analysis, there does appear to be diagnostic benefit in adding PET scans to the work-up of suspected PNS with negative conventional imaging.

The presence of onconeural antibodies did not appear closely linked to PET scan findings. While 34 patients had positive PET scans, only 10 of these patients tested positive for onconeural antibodies. These results are limited, however, as neither study performed a full onconeural antibody panel. Hadjivassiliou et al. [8] only tested for Anti-Hu, Anti-Yo, and Anti-Ri with voltage gated calcium and potassium antibodies and amphiphysin antibodies in selected patients. Rees et al. [9] only tested for Anti-Hu and Anti-Yo. In addition, 62 patients in the meta-analysis had an unspecified antibody status, limiting the interpretation of the data. Several other studies have selected patients based on positive onconeural antibody status [10,11]. While these studies displayed a higher rate of abnormal PET findings, ranging from 70% to 90%, as well as high detection rates, the fact that 68% of patients with abnormal PET findings in our analysis were antibody negative does raise concerns about omitting this group. It is established that a proportion of patients with PNS will be antibody negative [12]; therefore, limiting access to PET scans based on antibody status does not seem reasonable.

Interpretation of the data is limited by the low number of studies that address our question, as well as the observational design of the studies and resulting risk of bias. Moreover, neither study used standardized criteria to identify patients with possible PNS. In both studies, the suspicion of PNS was based on the clinical opinion of a neurologist. In 2004, a list of criteria for the diagnosis of PNS was published by Graus et al. [3]. Based on clinical presentation, antibody status and the presence of an underlying malignancy, patients could be grouped as having either possible or definite PNS. Rees et al. [9] was published in 2001 and therefore could not apply the criteria. While Hadjivassiliou et al. [8] did apply the criteria retrospectively, it was not a part of the initial inclusion criteria. The lack of a standardized definition of PNS may increase the risk of bias in these studies.

The optimal duration of follow-up and utility of repeat imaging are not addressed by these studies. The diagnosis of PNS may predate the identification of an underlying malignancy by many years [13]. The median duration of follow-up in Rees et al. [9] was 16 months. Hadjivassiliou et al. [8] stated that all patients were followed up prospectively until a definite diagnosis was reached, but did not report the median follow-up duration or range. Longer follow-up with serial PET imaging may be required to optimize detection of an underlying tumour. In 2011, a European Federation of Neurologic Societies task force published guidelines on screening for tumours in cases of suspected PNS [14]. Due to the paucity of literature on the subject, most recommendations were based on expert consensus. In cases where a malignancy was not identified with initial screening, repeat screening was recommended after three to six months, followed by every six months for four years. Whether to include serial PET scans was not addressed, and remains a topic for further research.

Technical differences in PET scans between the trials and the current standard in Ontario may impact the generalizability of the findings. Hadjivasilliou et al. [8] utilized a dual-headed gamma camera modified to perform PET imaging in combination with a low-dose CT for anatomical localization and attenuation correction. Rees et al. [9] utilized FDG-PET imaging with no CT component. Since the publication of these studies, there have been technical advances in PET imaging and, currently, FDG-PET is used in combination with CT imaging to create a single co-registered image (PET-CT). It is unclear whether this would significantly impact the diagnostic yield of the test in the setting of suspected PNS.

CONCLUSIONS

While our analysis is limited by the small number of observational studies with variations in methodology, both studies demonstrated concordant results. The overall detection rate of PET scanning was low; however, both the pooled sensitivity and specificity were high. There did not appear to be a specific group that had greater benefit from PET scans, although this is limited by a small number of patients. PNS can cause severe morbidity, and treatment options are limited. Given the importance of identifying an underlying malignancy in the prognosis and treatment of PNS, the minimal risk of PET scans to patients, and the high sensitivity and specificity of PET scans when screening for an underlying malignancy as demonstrated in this analysis, we recommend performing PET scans in patients with suspected PNS and negative conventional imaging, with or without positive onconeural antibodies.

INTERNAL REVIEW

The evidence summary was reviewed by the Director of the PEBC. The Working Group is responsible for ensuring the necessary changes are made.

Approval by the PET Ontario Steering Committee

After internal review, the report was presented to the Ontario PET Steering Committee. The committee reviewed the document and formally approved the document on May 18, 2017.

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- Sara Miller for copy editing.

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Appendix 1: Members of the Working Group and their COI declaration

Name	Affiliation	Declarations of interest
Craig Harlos, MD Neuro-oncology Fellow	CancerCare Manitoba	No conflict declared
Raymond Poon, MPH Health Research Methodologist	Department of Oncology, McMaster University, Juravinski Hospital Site	No conflict declared

Appendix 2: Literature Search Strategy

The search was conducted in MEDLINE (1946 to September 2016) and EMBASE (1974 to 2016 week 39) on September 27, 2016.

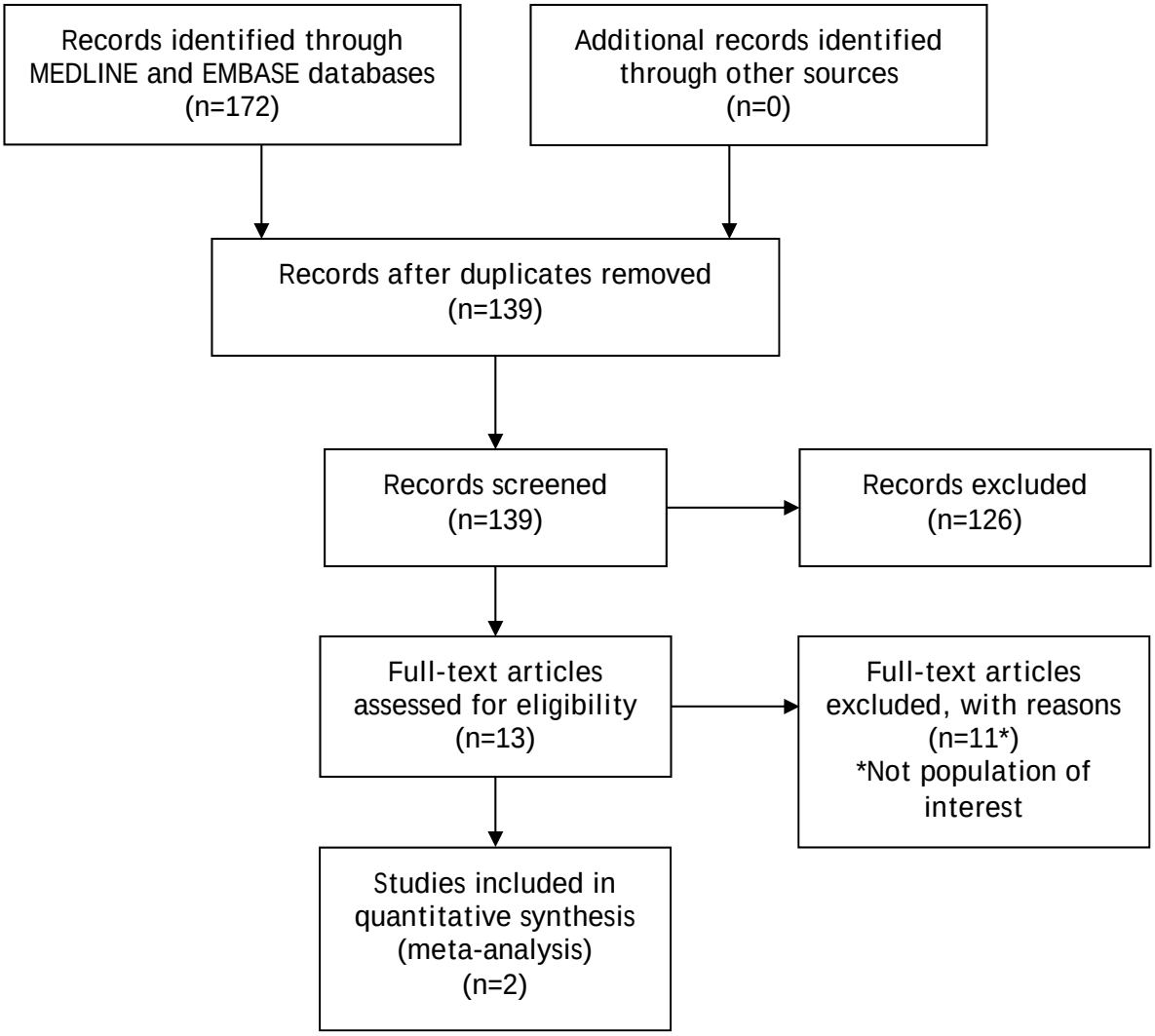
MEDLINE

Section A: Disease and/or population	1. cancer$.mp. or tumo?r$.mp. or carcinoma$.mp. or neoplas$.mp. or metastas$.mp. or malignan$.mp. or adenocarcinoma$.mp.
	2. ((neurologic$ or nervous system) and paraneoplastic and (syndrome? or disorder?)).mp.
	3. 1 and 2
Section B: Intervention or diagnostic test	4. exp Deoxyglucose/ or deoxyglucose.mp. or deoxy-glucose.mp. or fluorodeoxyglucose.mp. or 18fluorodeoxyglucose.mp. or fludeoxyglucose.mp. or fdg$.mp. or 18fdg.mp. or f-18-dg.mp. or fluoro-2-deoxy-d-glucose.mp. or 2fluoro-2deoxyglucose.mp. or fluoro-d-glucose.mp.
	5. exp Tomography, Emission-computed/
	6. (positron adj emission adj tomograph$).mp.
	7. (pet$ or pet scan$).mp.
	8. or/5-7
	9. (tomograph$ or ct scan$).mp.
	10. ct.mp.
	11. scan$.mp.
	12. 10 and 11
	13. 9 or 12
	14. 8 and 13
	15. (positron emission tomography computed tomography or pet ct or pet-ct or pet$ct).mp.
	16. 4 and (14 or 15)
Section C: Exclusion strategy	17. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
	18. animal/ not human/
	19. or/17-18
Combining Sections A, B, and C	20. 3 and 16
	21. 20 not 19
	22. limit 21 to English language

EMBASE

Section A: Disease and/or population	1. cancer$.mp. or tumo?r$.mp. or carcinoma$.mp. or neoplas$.mp. or metastas$.mp. or malignan$.mp. or adenocarcinoma$.mp. 2. ((neurologic$ or nervous system) and paraneoplastic and (syndrome? or disorder?)).mp. 3. 1 and 2
Section B: Intervention or diagnostic test	4. exp Deoxyglucose/ or deoxyglucose.mp. or deoxy-glucose.mp. or fluorodeoxyglucose.mp. or 18fluorodeoxyglucose.mp. or fludeoxyglucose.mp. or fdg$.mp. or 18fdg.mp. or f-18-dg.mp. or fluoro-2-deoxy-d-glucose.mp. or 2fluoro-2deoxyglucose.mp. or fluoro-d-glucose.mp.
	5. exp Tomography, Emission-computed/
	6. (positron adj emission adj tomograph$).mp.
	7. (pet$ or pet scan$).mp.
	8. or/5-7
	9. (tomograph$ or ct scan$).mp.
	10. ct.mp.
	11. scan$.mp.
	12. 10 and 11
	13. 9 or 12
	14. 8 and 13
	15. (positron emission tomography computed tomography or pet ct or pet-ct or pet$ct).mp.
	16. 4 and (14 or 15)
Section C: Exclusion strategy	17. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
	18. animal/ not human/
	19. or/17-18
Combining Sections A, B, and C	20. 3 and 16
	21. 20 not 19
	22. limit 21 to English language

Appendix 3: Modified PRISMA Flow Diagram



Appendix 4: QUADAS-2 Assessment of Study Quality

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Hadjivassiliou et al. 2009 [8]	L	L	U	H	L	L	L
Rees et al. 2001 [9]	L	L	U	H	L	L	L

L=Low Risk H=High Risk U=Unclear Risk