Original Article

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in the diagnosis of suspected paraneoplastic syndromes: A retrospective analysis

ABSTRACT

Paraneoplastic syndromes are a rare clinical presentation of tumor thought to affect 0.01% of patients with cancer. Paraneoplastic syndromes present a diagnostic challenge as a wide variety of signs and symptoms may appear. This study examines the use of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) as a diagnostic imaging tool for detecting tumor in suspected paraneoplastic syndrome cases. This single-center retrospective study included patients with suspected paraneoplastic syndrome who underwent whole-body ^{18}F-FDG PET/CT scan between December 2005 and December 2016. Associated clinical data were gathered via electronic chart review. Patient records were reviewed for age, sex, clinical signs and symptoms, ancillary diagnostic procedures, date of diagnosis, and follow-up time. Ninety-nine patients met inclusion criteria for this study. Mean follow-up period was 1.8 years. Cancer prevalence was 12.1%. The ^{18}F-FDG PET/CT results are as follows: 10 true positives, 5 false positives, 82 true negatives, and 2 false negatives. The diagnostic values are as follows: sensitivity 83.3%, specificity 94.3%, positive predictive value 66.7%, and negative predictive value (NPV) 97.6%. The high NPV in our study supports the effectiveness of ^{18}F-FDG PET/CT to rule out tumor in suspected paraneoplastic syndrome. Future research aims to analyze which patients with suspected paraneoplastic syndrome would benefit most from ^{18}F-FDG PET/CT.

Keywords: Oncology, paraneoplastic syndrome, positron emission tomography/computed tomography

INTRODUCTION

Paraneoplastic syndromes encompass a variety of signs and symptoms that are often present for months to years before detecting an underlying tumor, arising at a distance from the occult primary tumor or metastasis. These clinical manifestations are thought to be caused by an immunological response or by a biochemical substance, the former a result of ectopic antigen expression normally found in the nervous system.[1] Paraneoplastic syndromes can be caused by malignant, and less frequently benign, primary neoplasms. The clinical presentation of paraneoplastic syndromes can be divided into neurological and nonneurological syndromes. The nonneurological syndromes can be further subdivided into those affecting the dermatologic, gastrointestinal, endocrine, hematologic, and musculoskeletal systems. Biochemical abnormalities may be present. In many cases where an underlying etiology cannot be found, paraneoplastic syndromes are often included in the differential diagnosis, necessitating workup for tumor. The search for tumor is often hindered by the small size of culprit neoplasms.[2] While computed tomography (CT) scan is often first line in diagnostic assessment, CT relies on structural abnormalities and changes, characteristics

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which may not be seen with a small neoplasm. Moreover, evaluation of sites such as the cerebellum, spinal cord, and oral cavity is limited by poor soft tissue contrast of CT, and visualization of the oral cavity can be further limited by dental streak artifact.[3]

As a result, a whole-body positron emission tomography (PET) scan is a useful imaging tool in addition to a whole-body CT scan. PET involves injecting ^{18}F-fluorodeoxyglucose (^{18}F-FDG), a glucose analog labeled with the radioactive isotope fluorine-18. Intense ^{18}F-FDG uptake in localized areas signifies high metabolic activity, an indication of tumor, inflammation, and/or infection and therefore can play a role in assessing for a culprit neoplasm.[4] The European Federation of Neurological Societies recommends ^{18}F-FDG PET/CT when morphological imaging tests are negative.[5] This retrospective study assesses the use of ^{18}F-FDG PET/CT as a diagnostic tool in a group of suspected paraneoplastic syndrome patients in a North American tertiary care center.

MATERIALS AND METHODS

This single-center retrospective study included patients with suspected paraneoplastic syndrome who underwent a whole-body ^{18}F-FDG PET/CT scan between December 2005 and December 2016. The institutional electronic database was searched for the key terms "paraneoplastic" and "PET/CT," yielding 352 files. Duplicate files were removed, and patients were excluded if they had previously diagnosed tumor before the PET/CT scan. Each referral was reviewed manually by R. B. for inclusion in the study. Paraneoplastic syndromes were diagnosed by the referring physicians on the foundation of recommendation criteria[6] and following exclusion of other possible causes. Both neurological and nonneurological paraneoplastic syndromes were included. Patients who did not meet the recommendation criteria for paraneoplastic syndrome or were deemed by the referring physician to have a low likelihood of paraneoplastic syndrome were excluded. In a given patient with more than one relevant referral during the inclusion period, only data from the first PET/CT scan were used. No uniform paraneoplastic antibody markers or imaging studies were performed before the ^{18}F-FDG PET/CT scan. Associated clinical data were gathered via electronic chart review. Patient records were reviewed for age, sex, clinical signs and symptoms, further diagnostic procedures, date of confirmed diagnosis, and follow-up time. ^{18}F-FDG PET/CT findings were noted and compared to the presence of tumor at the last follow-up date.

A ^{18}F-FDG PET/CT scan was true positive if the suspected tumor was confirmed histologically. A false-negative occurred when the PET/CT scan did not indicate tumor, yet a tumor was confirmed histologically in the subsequent follow-up period. The ^{18}F-FDG PET/CT scan was false-positive when the scan was suspicious of tumor, yet further diagnostic procedures and follow-up period did not identify the presence of tumor. A scan was considered true-negative if the PET/CT was not suspicious of tumor and no tumor was identified in the subsequent follow-up period. The diagnostic values – sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were then calculated to evaluate the diagnostic ability of ^{18}F-FDG-PET/CT to assess tumor in suspected paraneoplastic syndrome. The study was approved by the Institutional Review Board vide their letter number 2017P000117/PHS dated January 25, 2017.

RESULTS

A total of 99 patients (55.6% male, average age 57.4 years) were included in this retrospective study. The mean follow-up period was 1.8 years. Patients were divided into subgroups based on clinical signs and symptoms [Table 1]: neurological (n = 87), neurological and abnormal biochemistry (n = 7), hematological (n = 2), dermatological (n = 2), and gastrointestinal (n = 1). These findings are listed in Table 1 along with the detailed signs and symptoms at presentation.

The cancer prevalence in our study was 12.1%. ^{18}F-FDG PET/CT was suspicious for tumor in 15 out of 99 cases (15.2%). Of the 15 cases, 10 had tumor confirmed by biopsy. ^{18}F-FDG PET/CT did not find tumor in 84 of 99 cases (84.8%). Of the 84 cases, 2 were found to have tumor during the follow-up period. These results culminated in 10 true positives, 82 true negatives, 5 false positives, and 2 false negatives. Therefore, the diagnostic values are as follows: sensitivity 83.3%, specificity 94.3%, PPV 66.7%, and NPV 97.6%.

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography-diagnosis of tumor

^{18}F-FDG PET/CT correctly identified 10 of 12 patients with tumor. Patients presented with neurological (n = 7), neurological + abnormal biochemistry (n = 1), hematological (n = 1), and gastrointestinal (n = 1) symptoms. The tumors found include squamous cell carcinoma of lung (n = 1), squamous cell carcinoma of unknown origin (n = 1), ovarian teratoma (n = 1), serous adenocarcinoma (n = 1), papillary thyroid carcinoma (n = 1), invasive ductal carcinoma of the breast (n = 1) [Figure 1], small cell carcinoma of lung (n = 1) [Figure 2] atypical mesothelioma (n = 1) [Figure 3], neuroendocrine carcinoma (n = 1), and transitional cell carcinoma of the bladder (n = 1). Two cases, the squamous cell carcinoma of lung and transitional cell carcinoma of the bladder, were determined not to be causing paraneoplastic

syndrome, as symptoms failed to improve after treatment of the tumor. These findings are shown in Table 2.

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography-misdiagnosis of tumor

The ^{18}F-FDG-PET/CT was false-negative in two patients who both presented with neurological symptoms and abnormal biochemistry. The patients were found to have an ovarian teratoma and renal oncocytoma, respectively, during the follow-up period.

The ^{18}F-FDG PET scan was classified as being false-positive in 5 cases. Three patients had abnormal ^{18}F-FDG uptake in the gastrointestinal tract or neighboring lymph nodes. The remaining two patients had suspicion for tumor in the pancreatic head and right kidney, respectively. Further diagnostic tests did not identify a tumor in the follow-up period. Table 3 conveys the interrelationship between paraneoplastic syndrome symptoms, ^{18}F-FDG PET/CT findings, and further diagnostic procedures.

DISCUSSION

The strengths of this study include a large heterogeneous patient cohort and long follow-up period. The cancer

Table 1: Paraneoplastic syndrome signs and symptoms

Symptoms	*n*	Symptoms	*n*	Symptoms	*n*
Neurological		Neurological + abnormal biochemistry		Hematological	
Brainstem encephalitis	1	Hyponatremia/SIADH + seizures	2	Neutropenia	1
Polyneuropathy	20	Anti-NMDA receptor antibodies + Seizures	4	Lymphocytic predominance on LP	1
Chorea	1	Anti-GFAP antibody + Ataxia	1	Total	2
Ocular flutter	2	Total	7		
Ataxia	21				
Ataxia + neuropathy	11				
Stiff person syndrome	1				
Optic neuropathy	1				
Nystagmus	3				
Nystagmus + optic neuropathy	1				
Nystagmus + ataxia	1				
Seizure	13				
Seizures + ataxia	1				
Guillain-Barré syndrome	1				
Miscellaneous	9				
Total	87				
Dermatological		Gastrointestinal			
Pemphigus foliaceus	1	Chronic intestinal pseudo-obstruction	1		
Jaundice	1	Total	1		
Total	2				

SIADH: Syndrome of inappropriate antidiuretic hormone secretion; NMDA: N-methyl-D-aspartate; GFAP: Glial fibrillary acidic protein; LP: Lumbar puncture

Table 2: Patients with confirmed tumor

Subgroup	Signs/symptoms	^{18}F-FDG PET/CT versus final diagnosis	Clinical diagnosis
Neurological	Ataxia	True positive	Serous adenocarcinoma
Neurological	Optic neuropathy + Nystagmus	True positive	Atypical mesothelial proliferation of the lung
Neurological	Miscellaneous	True positive	Transitional cell carcinoma of bladder*
Neurological	Seizure	True positive	Papillary thyroid carcinoma
Neurological	Ataxia + Neuropathy	True positive	Squamous cell carcinoma of lung*
Neurological	Ataxia + Neuropathy	True positive	Squamous cell carcinoma
Neurological	Ataxia + Nystagmus	True positive	Neuroendocrine carcinoma
Neurological + abnormal biochemistry	Seizure + Anti-NMDA receptor antibodies	True positive	Ovarian teratoma
Hematological	Lymphocytic predominance on LP	True positive	Small cell carcinoma of the lung
Gastrointestinal	Intestinal pseudo-obstruction	True positive	Invasive ductal carcinoma of the breast
Neurological + abnormal biochemistry	Seizure + Anti-NMDA receptor antibodies	False negative	Ovarian teratoma
Neurological + abnormal biochemistry	Seizure + hyponatremia	False negative	Renal oncocytoma

*^{18}F-FDG PET/CT finding of tumor unrelated to paraneoplastic syndrome, as symptoms failed to improve after treatment of the tumor. NMDA: N-methyl-D-aspartate; LP: Lumbar puncture; ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography

prevalence was 12.1%, which is similar with other studies [Table 4],[7-15] although slightly higher than Kristensen *et al*. who also excluded patients with previously diagnosed tumors from their group composition and reported a cancer prevalence of 8.8%.[7] Our prevalence may be in the higher range due to a greater proportion of suspected paraneoplastic syndrome cases (88% vs. 49%) and possibly higher pretest probability as other differentials were extensively investigated before the ^{18}F-FDG PET/CT scan was used. Our study has a similar composition to Vaidyanathan *et al*. with a slightly larger neurological subgroup (88% vs. 81%).[8] Our results follow similar trends to previous studies [Table 4], with moderate-high sensitivities, high specificities, very high NPV, and moderate PPV.

The major strength of the ^{18}F-FDG-PET/CT scan in suspected paraneoplastic syndrome cases lies in its ability to rule out disease, shown by the very high NPV (98%). Schramm *et al*. found that ^{18}F-FDG PET/CT is a useful single-combined modality tool for ruling out tumor, especially in sick patients with rapid clinical deterioration. In a per-patient analysis, sensitivity and specificity for neoplastic findings were 100% and 90% for ^{18}F-FDG PET/CT, compared to 78% and 88% for contrast-enhanced CT alone.[12] Moreover, the ^{18}F-FDG PET/CT scan can identify patients with incidental tumors that are unrelated to the paraneoplastic syndrome. Two of our patients (one squamous cell carcinoma of the lung and one transitional cell carcinoma) had neoplastic findings unrelated to the paraneoplastic syndrome but still held significant implications for the patients' health.

A major weakness of the ^{18}F-FDG PET/CT scan in evaluating for tumor in suspected paraneoplastic syndrome is its low sensitivity for certain tumors, particularly those that are small and occur in regions of high physiological ^{18}F-FDG activity. ^{18}F-FDG PET/CT is not recommended for primary detection of ovarian cancer, bladder and kidney tumors, hepatocellular carcinomas smaller than 5 cm in diameter, and early-stage lung cancer.[16-19] The ^{18}F-FDG PET/CT was not suspicious for two patients in our study who were found to have an ovarian teratoma and renal oncocytoma, respectively, in the subsequent follow-up period. Despite this, ^{18}F-FDG PET/CT remains a superior diagnostic imaging tool for anatomical localization and lesion characterization compared to the conventional CT scan.[10]

Another drawback of the ^{18}F-FDG PET/CT scan is the high false-positive rate and low PPV. There is normal physiological uptake of ^{18}F-FDG in the brain, heart, liver, spleen, gastrointestinal tract, urinary collecting system, and bone marrow that may be confused for pathology (i.e., tumor, inflammation, and infection) and lead to unneeded diagnostic

Table 3: False-positive ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography results

Subgroup	Signs/symptoms	Sites of abnormal ^{18}F-FDG uptake	Further diagnostic procedures
Neurological	Polyneuropathy	Multiple mediastinal and periesophageal lymph nodes	Endoscopic ultrasound
Neurological	Polyneuropathy	Right kidney	Kidney biopsy
Neurological + abnormal biochemistry	Seizure + anti-NMDA receptor antibodies	Duodenum	Esophagogastroduodenoscopy
Neurological	Ataxia	Pancreatic head	Pancreatic biopsy
Neurological	Seizure	Distal esophagus, colon	Esophagogastroduodenoscopy, colonoscopy

^{18}F-FDG: ^{18}F-fluorodeoxyglucose; NMDA: N-methyl-D-aspartate

Table 4: Similar ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography studies for comparison

	Paraneoplastic syndrome symptom(s)	Number of patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence (%)
Our study	Heterogeneous	99	83	94	66	98	12.1
Kristensen *et al*.[7]	Heterogeneous	137	75	83	29	97	8.8
Vaidyanathan *et al*.[8]	Heterogeneous	68	100	82	42	100	11.8
Selva-O'Callaghan *et al*.[9]	Dermatomyositis/polymyositis	55	67	98	86	94	-
McKeon *et al*.[10]	Neurological	56	100	74	46	100	17.8
Bannas *et al*.[11]	Neurological	46	100	86	40	100	8.7
Schramm *et al*.[12]	Neurological	66	100	90	-	-	13.6
Lebech *et al*.[13]	Heterogeneous	95	83	96	83	96	18.9
Sheikhbahaei *et al*.[14] (meta-analysis)	Heterogeneous	-	77	89	-	-	-
García Vicente *et al*.[15] (meta-analysis)	Heterogeneous	-	87.7	87	-	-	-

PPV: Positive predictive value; NPV: Negative predictive value

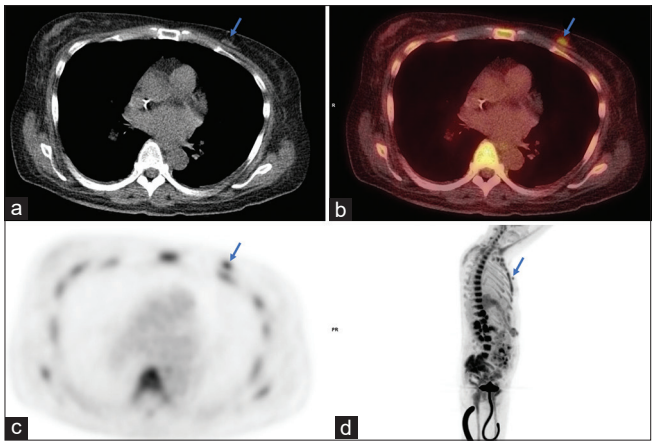

Figure 1: A 55-year-old woman with chronic intestinal pseudo-obstructions, fever, nausea, vomiting, and diarrhea. ^{18}F-FDG PET/CT scan shows (a) nodular opacity in the medial left breast on CT, with (b-d) intense ^{18}F-FDG uptake (arrow). Gastrointestinal symptoms gradually resolved after patient underwent surgery, chemotherapy, and radiation therapy for invasive ductal breast carcinoma

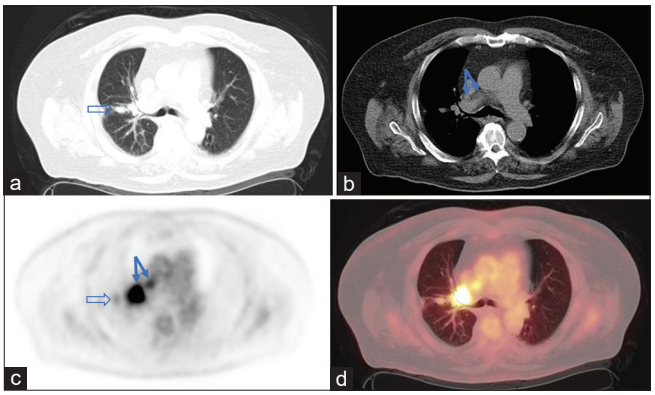

Figure 2: A 76-year-old man with new-onset nystagmus, altered mental status, and unsteady gait. Brain magnetic resonance imaging (not shown) was without acute abnormality. (a) CT scan shows a small right upper lobe nodule (open arrow), and (b) lymphadenopathy in the right hilum and mediastinum (arrows). (c and d) ^{18}F-FDG PET/CT scan shows moderate uptake in the lung nodule (open arrow) and intense uptake in the hilar and mediastinal lymph nodes (arrows). Biopsy of lymph node revealed metastatic small cell lung carcinoma

procedures.[20] In our study, there were five false positives which led to a variety of further procedures which may have been superfluous in retrospect. On the other hand, an esophageal ultrasound in one patient led to the diagnosis of esophagitis with ulceration. In future, a larger risk–benefit analysis could be beneficial in determining the need for further testing.

Two recent meta-analyses have been published on the use of ^{18}F-FDG PET scan in suspected paraneoplastic syndrome.[14,15] The study published by Sheikhbahaei *et al*. in recent systematic review and meta-analysis of ^{18}F-FDG PET and ^{18}F-FDG PET/CT in patients with paraneoplastic syndrome demonstrated a pooled sensitivity of 0.81, specificity of 0.88, and moderate diagnostic odds ratios (DOR). The area under the curve (AUC) of the summary receiver operating characteristic curve was 0.916. While the studies were heterogeneous, a secondary analysis excluding studies with high degrees of bias yielded an AUC of 0.931. A false-negative rate was seen as 19%, suggesting the need for ongoing screening at 3–6 month intervals following a negative study. Patients with positive paraneoplastic antibodies tended to have more diagnostically accurate scans. However, the presence of onconeural or classic antibodies did not affect the diagnostic performance of PET. Both studies' conclusions indicated that ^{18}F-FDG PET and ^{18}F-FDG PET/CT have excellent diagnostic accuracy with moderate sensitivity/specificity.

Comparison of our results to these published meta-analyses is difficult, as the evaluated prior studies comprised of heterogeneous individuals with varying degrees of pretest suspicion of paraneoplastic syndrome. In addition, those studies used varying imaging protocols, some using PET/CT and others PET only. However, the overall sensitivity and specificity of ^{18}F-FDG PET/CT reported in these meta-analyses of 77%–87.7% and 87%–89%, respectively, are comparable to our results, and the authors of both studies conclude that ^{18}F-FDG PET/CT has a high diagnostic performance for detection of underlying tumor syndrome. Our study demonstrated a very high NPV not seen in the meta-analysis. Explanation for this could be due to our diagnostic workup before PET scan, which would confer a patient selection bias. The heterogeneity of tumor type may also have played a role. Methodology with respect to pretest suspicion is also highly variable.

Further research is needed to classify patients who would most benefit from a ^{18}F-FDG PET/CT. Bannas *et al*. suggest testing for paraneoplastic antibodies (anti-Hu, anti-Yo, anti-CV2/CRMP5, anti-Ri, anti-Ma2, etc.,) before considering paraneoplastic syndrome as a differential diagnosis.[11]

The European Federation of Neurological Sciences published a framework for the use of ^{18}F-FDG PET/CT in suspected paraneoplastic syndrome, suggesting that other imaging modalities (US, CT) should be performed before the use of PET/CT.[5] However, we feel this could lead to potential delay in diagnosis and definitive management, and a ^{18}F-FDG PET/CT should be initially considered to rule out tumor.

The major limitation of our study is its retrospective nature. In addition, the ^{18}F-FDG PET/CT scans were read by a group of radiologists ($n = 7$) from a single institution that may lead to variability in the interpretation of ^{18}F-FDG-avid sites. Although the average follow-up period in our study was relatively long compared to previously published studies, the time between

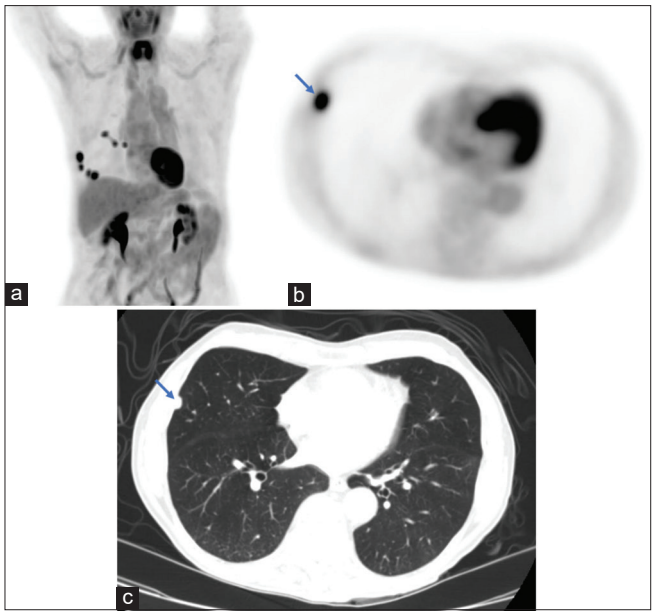

Figure 3: An 88-year-old man with new-onset diplopia, nausea, and unsteady gait. Brain magnetic resonance imaging (not shown) was without acute abnormality. (a) ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography scan maximum intensity projection image demonstrates multiple intensely ^{18}F-fluorodeoxyglucose-avid right pleural nodules. (b and c) Pleural nodule (arrow) was biopsied, revealing malignant mesothelioma

paraneoplastic syndrome onset and diagnosis of underlying tumor has been found to be as long as 8 years.[21]

CONCLUSION

Overall, the very high NPV found in our study supports the role of ^{18}F-FDG PET/CT as a diagnostic imaging modality to evaluate for the presence or absence of tumor in suspected paraneoplastic syndrome. Note is made however that the duration of follow-up, in this study – 1.5 years, can affect the NPV. Over a longer follow-up period, occult neoplasms can become apparent thus raising the false-negative rate and lowering the NPV. An advantage of ^{18}F-FDG PET/CT is that it can identify patients with incidental tumors and other abnormalities that are unrelated to the paraneoplastic syndrome. A drawback of ^{18}F-FDG PET/CT is the relatively low PPV that may lead to unnecessary diagnostic procedures. In future, patients could benefit from larger studies into implementation of cost-benefit analysis when considering further diagnostic procedures. In addition, such an analysis would more clearly identify which patients with suspected paraneoplastic syndrome would most benefit from ^{18}F-FDG PET/CT.

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Conflicts of interest

There are no conflicts of interest.

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