REVIEW ARTICLE

The Utility of Positron Emission Tomography in Epilepsy

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ABSTRACT: The role of fludeoxyglucose F 18 positron emission tomography (PET) in the presurgical evaluation of patients with medically intractable epilepsy continues to be refined. The purpose of this study was to systematically review the literature to assess the diagnostic accuracy and utility of PET in this setting. Thirty-nine studies were identified through MEDLINE and EMBASE databases that met the inclusion criteria. In adult patients, PET hypometabolism showed a 56 to 90% agreement with seizure onset localized by intracranial electroencephalogram (pediatric: 21 to 86%). In temporal lobe epilepsy patients with good surgical outcome, PET displayed moderate to high sensitivity in localizing the seizure focus (range: 71 to 89%). The sensitivity increased by 8 to 23% when PET results were combined with magnetic resonance imaging or electroencephalogram. PET has been shown to affect patient management by improving the guidance of intracranial electrodes placement, altering the decision to perform surgery, or excluding patients from further evaluation.

RÉSUMÉ: Utilité de la tomographie par émission de positons dans l'épilepsie. Le rôle de la tomographie par émission de positons (PET scan) au 18F fluodésoxyglucose (18F-FDG) dans l'évaluation préchirurgicale de patients présentant une épilepsie réfractaire au traitement médical est constamment raffiné. Le but de cette étude était de revoir systématiquement la littérature afin d'évaluer la précision du diagnostic et l'utilité du PET scan dans ce contexte. Nous avons identifié 39 études dans les bases de données MEDLINE et EMBASE qui rencontraient nos critères d'inclusion. Chez les patients adultes, un hypométabolisme au PET scan concordait entre 56 et 90% avec le début de la crise localisé par l'électroencéphalographie intracrânienne (patients pédiatriques: entre 21 et 86%). Chez les patients atteints d'épilepsie temporale chez qui le résultat chirurgical avait été favorable, le PET scan avait une sensibilité de modérée à élevée pour localiser le foyer épileptogène (écart : 71 à 89%). La sensibilité augmentait de 8 à 23% quand les résultats du PET scan étaient combinés à l'imagerie par résonance magnétique ou à l'électroencéphalographie. Il est démontré que le PET scan influence le traitement du patient en améliorant le guidage lors de la mise en place des électrodes intracrâniennes, en modifiant la décision de procéder à une chirurgie ou en évitant de procéder à des examens plus poussés chez certains patients.

Keywords: Electroencephalography, epilepsy, epilepsy - pediatric, epilepsy surgery, positron emission tomography

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INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures. In Canada, the prevalence of self-reported epilepsy ranges from 5.2 to 5.6 cases per 1000 population.[1] Every year, approximately 15,500 new patients are diagnosed with this condition.[2] For most individuals affected by epilepsy, seizures can be brought under control by drug therapy; however, up to 20-30% of patients do not respond to medication and surgical resection of the epileptic focus may be considered.[3] The initial stage of the workup for surgery usually involves a series of tests to isolate the brain region responsible for the occurrence of seizures. Standard assessment consists of history and physical examination, prolonged scalp video-electroencephalogram (EEG) in an epilepsy monitoring unit, magnetic resonance imaging (MRI) of the brain, and neuropsychological testing. When there is a clear lesion and the video-EEG results coincide with the MRI lesion, patients will undergo surgical resection of the epileptogenic focus. But, in those cases where the information obtained is not concordant or does not provide an accurate localization, intracranial placement of electrodes and subsequent video-EEG (intracranial EEG) may be indicated. Currently, noninvasive studies provide information to guide the placement of intracranial EEG electrodes. If the seizure focus is localized, surgery is considered. Precise presurgical localization of the seizure focus is essential to achieving good surgical outcomes.

Despite the long-standing application of fludeoxyglucose F 18 (^{18}F-FDG) positron emission tomography (PET) in the presurgical evaluation of patients with medically intractable epilepsy, the role of this technology continues to be refined with usage differing among providers and institutions. PET has the unique capability of imaging cerebral metabolism, whereas EEG measures electrical activity and MRI depicts only gross anatomic alterations associated with epilepsy. Each test is of clinical value and can provide information that can be used for all levels of surgical decision-making. Several reports in the past have indicated that PET is safe and may benefit a subset of patients undergoing surgery,[4-6] whereas another report concluded that there is a lack of evidence on the effectiveness

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and cost-effectiveness of imaging techniques (including PET) in the presurgical workup to inform clinical practice.[7] As a result, the purpose of the present study was to systematically review the literature to assess the diagnostic accuracy and clinical utility of PET in the presurgical evaluation of adult and pediatric patients with medically intractable epilepsy.

Methods

The literature was searched using MEDLINE (1946 to September week 4 2013) and EMBASE (1974 to 2013 week 29) databases in OVID. The search strategy combined disease-specific terms (exp epilepsy/or epilep$.ti,ab.) with intervention-specific terms (exp tomography, emission computed/ or pet or positron emission tomograph$ or positron-emission),ti, ab.). In addition, annual meetings of the American Epilepsy Society were searched up to September 2013 for other relevant abstracts. Likewise, the Canadian Medical Association Infobase, the National Guidelines Clearinghouse, and the Cochrane Database of Systematic Reviews were searched up to September 2013 for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these were searched for additional studies, as were the reference lists from relevant review articles.

The following criteria were used to include studies: (1) fully published reports or abstracts of systematic reviews, randomized controlled trials, and prospective or retrospective studies that evaluated the use of ^{18}F-FDG PET in medically intractable epilepsy; (2) studies that included ≥12 patients of any age; (3) reported on at least one of the following outcomes: diagnostic accuracy (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]), surgical management impact, or patient outcome impact; and (4) studies that used a suitable reference standard (intracranial EEG, surgical eligibility, good surgical outcome [Engel class I, II, or III]) when appropriate. The exclusion criteria were (1) studies of non–^{18}F-FDG PET; (2) nonsystematic reviews, letters, editorials, individual case reports, historical articles, or commentaries; and (3) reports published in a language other than English. An assessment of study quality was performed for all fully published reports by one reviewer.

Results

No existing systematic reviews or evidence-based guidelines were found that specifically evaluated the use of ^{18}F-FDG PET against a suitable reference standard. In addition, there were no randomized controlled trials comparing the diagnostic accuracy and clinical utility of ^{18}F-FDG PET with intracranial EEG. However, 37 retrospective studies[8-43,44] and three prospective studies[45-47] were identified to be relevant to this systematic review (Figure 1). Six of these studies were reported solely in abstract form,[17,24,25,34,38,41] whereas two studies[30,33] had both the full publication and the abstract. Because of the heterogeneity of the studies in the patient population, study design, outcome measurements, and methods of PET interpretation, the results of the studies included in the systematic review could not be pooled. Instead, a qualitative analysis of the results was performed.

Study Design and Quality

For the fully published reports, study quality was assessed using the QUADAS-2 tool (Table 1). Abstracts were not assessed because of limited reporting of study information. The overall quality varied among the studies, but the large majority were judged to have a low risk of bias. The most common concern was the influence of PET results on the interpretation of the reference standard. That is, localization with intracranial EEG, decision to perform surgery, and classification of surgical outcomes were often not blinded to PET findings. Furthermore, some studies excluded patients with MRI abnormalities (i.e. structural lesions),[13,16,19,21,37,46,47] incomplete tests or short follow-up,[39] lost to follow-up,[19] or a definite extratemporal seizure origin.[26]

Diagnostic Accuracy

Comparison with Intracranial EEG

There were eight retrospective studies identified that investigated the localization of seizure foci with PET compared with intracranial EEG in adult patients.[31-37,46] These studies included patients with temporal and/or extratemporal lobe epilepsy. One of the studies[31] reported positive correlation between PET and

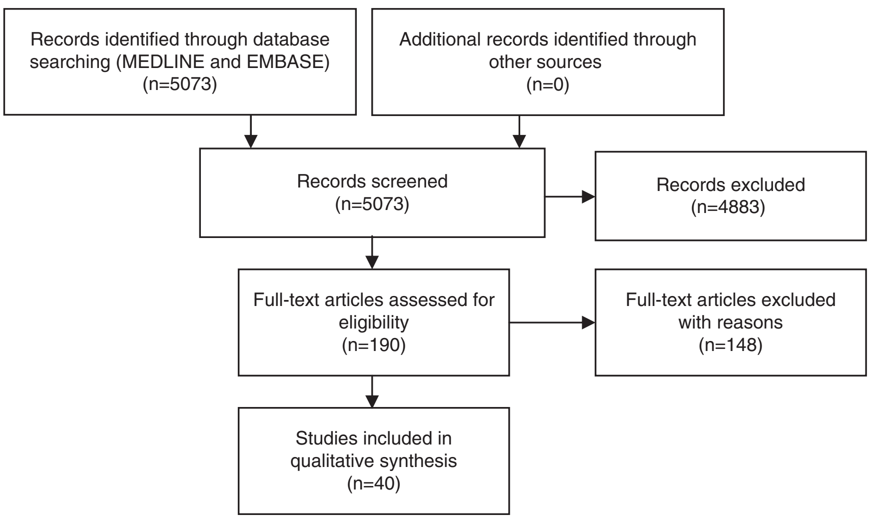

Figure 1: *Literature flow diagram.*

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Table 1: QUADAS-2 assessment of study quality

	Risk of bias				Applicability concerns		
Study	**Patient selection**	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Reference standard**
Comparison between ^{18}F-FDG PET and intracranial EEG in the localization of seizure foci							
Debets et al, 1990[31]	U	L	L	L	U	L	L
Delbeke et al, 1996[32]	L	L	L	H	L	L	L
Desai et al, 2013[33]	L	U	H	L	L	L	L
Sadzot et al, 1992[35]	U	L	H	L	U	L	L
Tatlidil et al, 2000[36]	L	L	H	L	L	L	L
Theodore et al, 1997[47]	H	L	L	L	H	L	L
Van Huffelen et al, 1990[37]	H	L	H	L	H	L	L
Kumar et al, 2010[23]	L	L	L	L	L	L	L
Seo et al, 2011[39]	H	U	H	L	H	L	L
Seo et al, 2009[40]	L	U	L	L	L	L	L
Diagnostic accuracy of ^{18}F-FDG PET with respect to surgery							
Dellabadia et al, 2001[21]	H	L	H	L	H	L	L
Mastin et al, 1996[22]	L	L	H	L	L	L	L
Struck et al, 2011[42]	L	L	H	H	L	L	L
Diagnostic accuracy of ^{18}F-FDG PET in patients with good surgical outcome							
Heinz et al, 1994[8]	L	L	H	L	L	L	L
Hong et al, 2002[9]	L	L	H	L	L	L	L
Hwang et al, 2001[10]	L	L	H	L	L	L	L
Kassem et al, 2013[11]	L	L	H	L	L	L	L
Kim et al, 2004[12]	L	L	H	H	L	L	L
Kim et al, 2002[13]	H	L	H	L	H	L	L
Knowlton et al, 2008[45]	L	L	H	L	L	L	L
Kun Lee et al, 2005[14]	L	L	H	L	L	L	L
Lee et al, 2008[15]	L	L	H	L	L	L	L
Lee et al, 2005[16]	H	L	H	L	H	L	L
Won et al, 1999[18]	L	L	H	L	L	L	L
Yun et al, 2006[19]	H	L	H	L	H	L	L
Kim et al, 2009[20]	U	L	H	L	U	L	L
Widjaja et al, 2013[46]	H	L	L	L	H	L	L
Impact of ^{18}F-FDG PET on patient management							
Uijl et al, 2007[26]	H	L	H	L	H	L	L
Chugani and Conti, 1996[27]	L	L	U	U	L	L	L
Ollenberger et al, 2005[28]	L	L	L	L	L	L	L
Snead et al, 1996[431]	L	L	H	L	L	L	L
Impact of ^{18}F-FDG PET/MRI coregistration on patient management							
Salamon et al, 2008[29]	L	L	U	U	L	L	L
Rubi et al, 2011[30]	L	L	H	L	L	L	L
Chassoux et al, 2010[44]	L	L	H	L	L	L	L

H, high risk; L, low risk; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; U, unclear risk.

intracranial EEG for both localization (59%) and lateralization (18%) of onset. That is, using intracranial EEG as the reference standard, PET correctly identified the epileptogenic lobe in 59% of the patients and the epileptogenic side, but not the lobe in 18% of the patients. Another study reported a sensitivity of 77% for lateralization only.[36] Overall, the sensitivity at which PET hypometabolism agreed with seizure onset localized by intracranial EEG ranged from 56% to 90% (weighted mean = 71%).

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Among studies that included only temporal lobe epilepsy patients,[32,34,47] the sensitivity of PET ranged from 63% to 90% (weighted mean = 74%) (Table 2).

In pediatric patients with intractable epilepsy of both temporal and extratemporal origins, four primary studies were identified that compared PET with intracranial EEG in the localization of seizure foci.[23,38-40] In one study,[23] the results for two methods of PET interpretation—visual analysis (V) and statistical parametric mapping (SPM)—were reported. SPM using a threshold of $p < 0.001$ provided a sensitivity of 86% when measured against intracranial EEG. The sensitivity decreased to 60% after using a stricter threshold of $p < 0.05$. In comparison, the sensitivity for V was 74%. Another study[39] reported lobar concordance between PET and intracranial EEG in 21% of the patients and hemispheric but not lobar concordance in 50% of the patients. In general, the sensitivity of PET localization with respect to intracranial EEG varied from 21% to 86% (weighted mean = 68%) across the four studies (Table 3).

Table 2: Comparison between ^{18}F-FDG PET and intracranial EEG in the localization of seizure foci (adult)

Study	Study type	Patient population	PET interpretation	Reference standard	Sensitivity localization*	Sensitivity lateralization†
Debets et al, 1990[31]	Retrospective	22 patients with medically intractable complex partial seizures	V, Q	Intracranial EEG	59% (13/22)	18% (4/22)
Delbeke et al, 1996[32]	Retrospective	38 patients with uncontrolled partial seizures	SQ	Intracranial EEG	86% (19/22)	NR
Desai et al, 2013[33]; Desai et al, 2012 (abstract)[51]	Retrospective	53 patients with medically refractory epilepsy	V	Intracranial EEG	56% (25/45)	NR
Eddeine and Chung, 2012 (abstract)[34]	Retrospective	42 TLE patients with normal MRI and sufficient seizures for ictal-focus localization	NR	Intracranial EEG	90% (9/10)	NR
Sadzot et al, 1992[35]	Retrospective	57 patients with drug-resistant complex partial epilepsy considered for surgery	V, Q	Intracranial EEG	88% (28/32)	NR
Tatlidil et al, 2000[36]	Retrospective	35 patients who underwent an anterior temporal lobectomy for complex partial seizures	SQ	Intracranial EEG	NR	77% (10/13)
Theodore et al, 1997[47]	Prospective	46 patients with uncontrolled complex partial seizures not localized by ictal surface-sphenoidal video-EEG	Q	Intracranial EEG	63% (25/40)	NR
Van Huffelen et al, 1990[37]	Retrospective	17 patients with medically intractable complex partial seizures and EEG lateralization of the epileptic focus	Q	Intracranial EEG	88% (7/8)	NR

BZ, benzodiazepine; NR, not reported; Q, quantitative; SPECT, single photon emission computed tomography; SQ, semiquantitative; TLE, temporal lobe epilepsy.

*Localization sensitivity = number of patients in whom PET localized the seizure focus that was concordant with intracranial EEG/total number of patients in whom the seizure focus was localized with intracranial EEG.

†Lateralization sensitivity = number of patients in whom PET lateralized (but not localized) the seizure focus that was concordant with intracranial EEG/ total number of patients in whom the seizure focus was localized with intracranial EEG.

Table 3: Comparison between ^{18}F-FDG PET and intracranial EEG in the localization of seizure foci (pediatric)

Study	Study type	Patient population	PET interpretation	Reference standard	Sensitivity localization*	Sensitivity lateralization†
Kumar et al, 2010[23]	Retrospective	20 children with intractable focal epilepsy, seizure free after surgery.	V, SPM ($p < 0.001$, $p < 0.0001$, $p < 0.05$)	Intracranial EEG	V: 74%‡ SPM: 60-86%‡	NR
Piantino and Hussein, 2011 (abstract)[38]	Retrospective	20 patients with medically refractory epilepsy who underwent surgery.	NR	Intracranial EEG	70% (14/20)	NR
Seo et al, 2011[39]	Retrospective	14 children with nonlesional intractable focal epilepsy	V, SPM	Intracranial EEG	21% (3/14)	50% (7/14)
Seo et al, 2009[40]	Retrospective	27 children with no detectable lesions on MRI and had undergone surgery	NR	Intracranial EEG	78% (21/27)	NR

MSI: Magnetic source imaging; NR: not reported.

*Localization sensitivity = number of patients in whom PET localized the seizure focus that was concordant with intracranial EEG/total number of patients in whom the seizure focus was localized with intracranial EEG.

†Lateralization sensitivity = number of patients in whom PET lateralized (but not localized) the seizure focus that was concordant with intracranial EEG/ total number of patients in whom the seizure focus was localized with intracranial EEG.

‡Values for numerator and denominator unavailable.

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With Respect to Surgical Decision Making

Four retrospective studies examined the contribution of PET to surgical decision-making for adult patients with medically intractable epilepsy.[21,22,41,42] Two of these evaluated only patients with temporal lobe epilepsy,[41,42] whereas in the other studies, patients with temporal and extratemporal lobe epilepsy were included.[21,22] Two studies[21,42] evaluated the predictive utility of PET on surgical eligibility. PET could accurately predict surgical candidacy in 68% (PPV) of the patients, which was equivalent to that of MRI and EEG. However, PET was the most sensitive (86%) and had the highest proportion of true-positive and true-negative tests (72%), whereas the sensitivity and proportion of true-positive and true-negative tests were 66% and 67%, respectively, for both MRI and EEG.[21] The second study also reported a sensitivity of 86% for PET, which was higher than that of EEG (82%) but lower than MRI (90%). Additionally, multivariate analysis revealed that PET hypometabolism was a significant predictor of postoperative outcome ($p = 0.02$).[42] Site of surgery was used as the reference standard in the other two studies.[22,41] The abstract by Khan et al[41] reported that 59% of the patients had either lateralizing or localizing PET findings corresponding to the resected seizure focus. The second study[22] reported a similar sensitivity of 60% as well as a PPV of 83% (Table 4). In most of the studies, consensus agreement based on all available clinical and diagnostic information was used to determine surgical candidacy or surgical sites.

One retrospective study evaluated the diagnostic performance of PET with respect to site of surgical resection in children with intractable epilepsy. Kumar et al[23] compared the results between V and SPM. The reported sensitivity from that study was 62% for V and 71% for SPM using a threshold of $p < 0.001$ (35% with a stricter threshold of $p < 0.05$). The specificity (V = 89%; $SPM_{p<0.001}$ = 86% to $SPM_{p<0.05}$ = 98%) and PPVs (V = 82%; $SPM_{p<0.001}$ = 79% to $SPM_{p<0.05}$ = 95%) were higher for both methods of analysis (Table 4). Resection margins were ultimately decided by intracranial EEG.

Patients with Good Surgical Outcome

In adult patients, a total of 13 primary studies used good surgical outcome to estimate the diagnostic accuracy of PET. Of these studies, 12 were retrospective[8-19] and one was part of a prospective observational study.[45] Good surgical outcome was considered in patients with Engel class I, II, or III. When outcomes were not reported by Engel's classification, seizure-free or significantly improved (<10 seizures per year and at least a 90% reduction in seizures from the preoperative year) was considered good surgical outcome. Two studies that included only patients with temporal lobe epilepsy[11,17] reported separate sensitivity values for the magnetic resonance–positive and magnetic resonance–negative subgroups. The results were similar between the studies for the magnetic resonance–positive (88% and 89%) and magnetic resonance–negative (80% and 81%) patients. Overall, the proportion of patients in whom PET correctly localized a seizure focus and had a good surgical outcome ranged from 36% to 89% (weighted mean = 68%). This range improved to 71% to 89% (weighted mean = 86%) when only considering patients with temporal lobe epilepsy.[8,11,17] In contrast, the sensitivity of PET ranged from 36% to 66% (weighted mean = 50%) in extratemporal lobe epilepsy patients only.[12-15] PET was able to further

Table 4: Diagnostic accuracy of ^{18}F-FDG PET with respect to surgery

Study	Study type	Patient population	Category	PET interpretation	Reference standard	Sensitivity*	Specificity†	PPV‡	NPV¶
Dellabadia Jr et al, 2002[21]	Retrospective	69 patients admitted for presurgical evaluation	Adult	V	Surgical candidacy	86%‖	59%‖	68%‖	80%‖
Khan et al, 2012 (abstract)[41]	Retrospective	99 anterior temporal lobectomy patients	Adult	NR	Resected seizure focus	59% (40/68)	NR	NR	NR
Mastin et al, 1996[22]	Retrospective	35 patients with intractable partial epilepsy who underwent surgery	Adult	V	Site of surgical resection	60% (15/25)	NR	83% (15/18)	NR
Struck et al, 2011[42]	Retrospective	124 patients with medically refractory TLE	Adult	NR	Surgical candidacy	86%‖	77%‖	NR	NR
Kumar et al, 2010[23]	Retrospective	20 children with intractable focal epilepsy	Pediatric	V, SPM ($p < 0.001$, $p < 0.0001$, $p < 0.05$)	Site of surgical resection	V: 62%‖ SPM: 35-71%‖	V: 89%‖ SPM: 86%-98%‖	V: 82%‖ SPM: 79%-95%‖	V: 73%‖ SPM: ª66-75%‖

ILAE, International League Against Epilepsy; NR, not reported; TLE, temporal lobe epilepsy.
*Sensitivity = number of surgical candidates with positive PET findings/total number of patients eligible for surgery (positive PET finding is defined as imaging abnormality in the area of surgical resection or conclusive evidence consistent with the final consensus decision regarding surgical candidacy).
†Specificity = number of patients considered ineligible for surgery on the basis of PET findings/total number of patients ineligible for surgery.
‡PPV = proportion of patients accurately predicted to be eligible for surgery.
¶NPV = proportion of patients accurately predicted not to be eligible for surgery.
‖Values for numerator and denominator unavailable.

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lateralize the seizure focus in 13% to 29% (weighted mean = 17%) of patients with a good surgical outcome.[9,12-15] In one study,[18] only the sensitivity for correct lateralization was reported (86%); therefore, it is not clear as to whether this is separate from or considered with localization. Lateralizing information gained from PET imaging is useful for planning an invasive study. In the only prospective study,[45] the authors reported a sensitivity of 59%, a specificity of 79%, a PPV of 83%, and a NPV of 54% for Engel class I outcome (Table 5). These diagnostic values were similar to magnetic source imaging (56% sensitivity, 79% specificity, 82% PPV, and 52% NPV).

In Engel class I pediatric patients, one prospective study[45] evaluated the sensitivity (65%), specificity (94%), PPV (68%), and NPV (94%) of PET relative to lobar localization. The corresponding values for magnetoencephalography were 85%, 99%, 94%, and 97%, respectively. However, if one or both of the two tests were concordant with cortical resection, the sensitivity increased to 95%. In one retrospective study,[41] PET showed a localizing sensitivity of 73% for temporal lesions and 63% for extratemporal lesions. The corresponding lateralizing sensitivities for temporal and extratemporal cases were 23% and 5%, respectively (Table 6).

Impact on Patient Management

18F-FDG PET

The evidence demonstrating the impact of PET on clinical management in adult patients came from three retrospective studies. In the Uijl et al study,[26] the impact of PET was assessed by comparing documented decisions regarding surgical candidacy before and after PET findings. The initial decision concerning whether to perform temporal lobe epilepsy surgery was based on MRI and video-EEG findings, and PET results led clinicians to change their decision in 71% (78 of 110) of the patients who underwent PET (of these 78 patients, 28 avoided surgery, 48 were considered for surgery [62% had Engel class I surgical outcome], and two were requested for intracranial monitoring [one was subsequently considered for surgery and had Engel class I surgical outcome, whereas surgery was ultimately not performed in the other). The abstract by Dickson et al[24] assessed the benefit of PET in the presurgical evaluation of 194 consecutive patients with medically refractory focal epilepsy. In this study, PET findings led directly to surgery in 6% of the cases, helped in planning intracranial EEG in 35% of the cases, and excluded 12% of the cases from additional evaluation. In another abstract by Popescu et al,[25] a preliminary study was undertaken to study the role of V and SPM analysis of PET in patients with temporal and extratemporal epilepsy. Results from the study showed that both methods of analysis helped improve the guidance of intracranial electrodes placement in 48% of the patients and ruled out stereo-EEG in 21% of the patients (Table 7).

There were three retrospective studies that provided evidence of a change in clinical management in pediatric patients because of PET. One study[27] investigated the effectiveness of PET in classifying symptomatic infantile spasms. With the benefit of PET, the number of cases classified as symptomatic increased from 30% to 96%. In other words, PET uncovered unifocal or multifocal metabolic abnormalities in 95% of the cryptogenic cases. In the study by Ollenberger et al,[28] the role of PET in the diagnosis and management of children with refractory epilepsy was assessed from the clinician's perspective. Three epileptologists completed the questionnaires in reference to 113 evaluable patients. For surgical candidates, PET scan results excluded surgery (major impact) in 39% of the patients and modified surgery (minor impact) in 19% of the patients. For medical therapy patients, PET resulted in surgery being excluded in 5% of the patients and management plan modified in 19% of the patients. The third study[43] compared children who received PET as part of epilepsy surgery evaluation (n = 56) with those who did not (n = 44). The authors reported that there was no significant difference between the two groups in terms of the number of children who underwent surgery, the type of procedure performed, the clinical outcome, or whether chronic invasive intracranial monitoring was needed. Of the 16 patients who had focal cortical resection or hemispherectomy, three avoided invasive monitoring because of localizing information provided by PET (Table 7).

18F-FDG PET/MRI coregistration

There were three primary studies that investigated the value of incorporating PET/MRI coregistration into the presurgical evaluation of patients with medically intractable epilepsy. The retrospective study by Salamon et al[29] compared two cohorts of patients with cortical dysplasia (CD), one in which PET/MRI coregistration was a routine part of the presurgical evaluation (n = 45) and the other without (n = 38). Compared with the patients before the regular use of PET/MRI coregistration, the cohort with the benefit of this technique had 18% more patients receiving surgery, a higher proportion of patients with type I CD on histopathology (60% versus 24%; p = 0.0009), and fewer patients undergoing intracranial electrode studies (2% vs 21%; p = 0.0060). In this same cohort, surgical resection guided by PET/MRI coregistration and electrocorticography resulted in 82% of the patients achieving seizure freedom. In another retrospective study involving children with refractory epilepsy,[30] PET/MRI coregistration guided the second MRI interpretation from non-lesional to subtle lesional in 42% of the cases. Similarly, PET/MRI coregistration was able to detect Taylor-type focal cortical dysplasia in patients with negative MRI and where a PET scan alone does not allow a conclusive diagnosis. Cortical resection guided by PET/MRI coregistration in addition to stereo-EEG led to 87% of patients achieving seizure freedom (Table 8).[44]

Discussion

In patients with medically intractable epilepsy, the main goal of presurgical evaluation is to provide precise localization of the epileptogenic focus with the intention of optimally selecting surgical candidates who are likely to have a seizure-free outcome after resective surgery. To date, no single test alone has been sufficient for localizing the surgical site and evaluation is based on a consensus of all available diagnostic information. Numerous scenarios arise in which intracranial EEG is necessary to provide critical data for patient management. However, intracranial EEG is an invasive procedure and poses the risk (although low) of infection, hemorrhage, and cerebral edema.[48] Particularly in children, the hospital stay is lengthened because of the time required to obtain the ictal onset and functional mapping information. With modern advances in structural and functional imaging, the ability to provide accurate information without the

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Table 5: Diagnostic accuracy of ^{18}F-FDG PET in patients with good surgical outcome (adult)

Study	Study type	Patient population	PET interpretation	Reference standard	Sensitivity* localization	Sensitivity lateralization†	Specificity‡	PPV¶	NPV‖
Heinz et al, 1994[8]	Retrospective	27 patients with medically intractable TLE	V	Seizure free or significantly improved#	71% (17/24)	NR	NR	NR	NR
Hong et al, 2002[9]	Retrospective	41 patients with nonlesional neocortical epilepsy patients who underwent surgical treatment	V	Engel class I-III	43% (12/28)	14% (4/28)	NR	NR	NR
Hwang et al, 2001[10]	Retrospective	117 patients with pathologically confirmed neocortical epilepsy who underwent surgical treatment	V	Engel class I-II	77% (61/79)	NR	NR	NR	NR
Kassem et al, 2013[11]	Retrospective	137 patients who received surgical treatment for intractable epilepsy	Q	Engel class I-II	MRI-positive: 88% (69/78)	MRI-negative: 80% (16/20)	NR	NR	NR
Kim et al, 2004[12]	Retrospective	40 patients diagnosed with parietal lobe epilepsy	SPM ($p<0.001$)	Seizure free	50% (7/14)	29% (4/14)	NR	NR	NR
Kim et al, 2002[13]	Retrospective	29 patients with FLE.	V, SPM ($p<0.005$, $p<0.001$)	Engel class I-II	V: 55% (16/29) SPM: 59% (12/29)-66% (19/29)	14% (4/29)	NR	NR	NR
Knowlton et al, 2008[45]	Prospective	62 patients with medically intractable partial epilepsy who completed ICEEG and subsequent surgical resection	V	Engel class I	59% (30/51)	NR	79%**	83%**	54%**
Kun Lee et al, 2005[14]	Retrospective	26 patients with OLE who underwent surgery.	V, SPM ($p<0.001$)	Seizure free	50% (8/16)	13% (2/16)	NR	NR	NR
Lee et al, 2008[15]	Retrospective	71 patients with intractable FLE who underwent epilepsy surgery	V, SPM	Engel class I	36% (12/33)	18% (6/33)	NR	63%**	45%**
Lee et al, 2005[16]	Retrospective	89 patients with intractable neocortical epilepsy and normal MRI who underwent focal surgical resection	SPM	Engel class I	58% (23/40)	NR	NR	NR	NR
Sucak et al, 2011 (abstract)	Retrospective	114 patients with TLE who underwent surgery	NR	Engel class I	Lesional: 89% (59/66) Nonlesional: 81% (13/16)	NR	NR	NR	NR
Won et al, 1999[18]	Retrospective	118 patients who underwent surgery for medically intractable epilepsy	V	Engel class I-II	NR	86% (68/79)	NR	NR	NR
Yun et al, 2006[19]	Retrospective	193 neocortical epilepsy patients who had undergone focal neocortical resection	V, SPM	Seizure free	63% (67/107)	NR	NR	NR	NR

FLE, frontal lobe epilepsy; ICEEG: intracranial EEG; NR, not reported; OLE, occipital lobe epilepsy; SPECT, single photon emission computed tomography.

*Localization sensitivity = number of patients in whom PET localized the seizure focus that was concordant with the surgical site and achieved good surgical outcome/total number of patients with good surgical outcome.

†Lateralization sensitivity = number of patients in whom PET lateralized (but not localized) the seizure focus that was concordant with the surgical site and achieved good surgical outcome/total number of patients with good surgical outcome.

‡Specificity = number of patients with negative PET findings and did not achieve good surgical outcome/total number of patients who did not achieve good surgical outcome (negative PET finding is defined as normal or multilobar pattern in both hemispheres).

¶PPV = proportion of PET positive patients accurately predicted to achieve good surgical outcome (positive PET finding is defined as imaging abnormality in the area of surgical resection or conclusive evidence consistent with the final consensus decision regarding surgical candidacy).

‖NPV = proportion of PET negative patients accurately predicted to not achieve good surgical outcome (negative PET finding is defined as normal or multilobar pattern in both hemispheres).

#Significantly improved is defined <10 seizures per year and ≥90% reduction in seizures from the preoperative year.

**Values for numerator and denominator unavailable.

Table 6: Diagnostic accuracy of ^{18}F-FDG PET in patients with good surgical outcome (pediatric)

Study	Study type	Patient population	PET interpretation	Reference standard	Sensitivity* localization	Sensitivity† lateralization	Specificity‡	PPV¶	NPV‖
Kim et al, 2009[20]	Retrospective	42 Engel Class 1 pediatric patients who received epilepsy surgery	NR	Engel class I	Extratemporal: 63% (12/19) Temporal: 73% (16/22)	Extratemporal: 5% (1/19) Temporal: 23% (5/22)	NR	NR	NR
Widjaja et al, 2013[46]	Prospective	22 children with nonlesional localization-related epilepsy who had surgical resection	V	Engel class I	65%#	NR	94%#	68%#	94%#

MEG, magnetoencephalography; NR, not reported; SISCOM, subtraction of ictal and interictal single photon emission computed tomography coregistered to MRI.
*Localization sensitivity = number of patients in whom PET localized the seizure focus that was concordant with the surgical site and achieved good surgical outcome/total number of patients with good surgical outcome.
†Lateralization sensitivity = number of patients in whom PET lateralized (but not localized) the seizure focus that was concordant with the surgical site and achieved good surgical outcome/total number of patients with good surgical outcome.
‡Specificity = number of patients with negative PET findings and did not achieve good surgical outcome/total number of patients who did not achieve good surgical outcome (negative PET finding is defined as normal or multilobar pattern in both hemispheres).
¶PPV = proportion of PET positive patients accurately predicted to achieve good surgical outcome (positive PET finding is defined as imaging abnormality in the area of surgical resection or conclusive evidence consistent with the final consensus decision regarding surgical candidacy).
‖NPV = proportion of PET negative patients accurately predicted to not achieve good surgical outcome (negative PET finding is defined as normal or multilobar pattern in both hemispheres).
#Values for numerator and denominator unavailable.

need for intracranial EEG has become increasingly important. In many patients, intracranial EEG can be avoided when data from less-invasive studies are concordant in their lateralization and localization.

FDG PET has been known to indirectly localize the seizure focus by determining areas of decreased glucose metabolism. A previous meta-analysis reported a concordance value of 67% between PET and invasive EEG recording.[49] This analysis included only patients with temporal lobe epilepsy and excluded pediatric patients. Still, data from this systematic review are consistent with their findings and showed a 56 to 90% agreement between PET hypometabolism and seizure onset localized by intracranial EEG among adults. Similar results were observed in pediatric patients except for one study that reported only 21% of patients in whom PET correctly localized the seizure focus when measured against intracranial EEG. However, PET was able to lateralize a further 71%. In the other studies, it was not possible to distinguish between localizing and lateralizing findings because this information is often hidden, not separated, or considered the same.

Despite the general acceptance of intracranial EEG as the gold standard for localizing the seizure onset, in clinical practice, the decision to proceed with surgery may come from a number of sources. Therefore, surgical candidacy or site of surgical resection was also considered as a reference standard for this review. Based on these studies, PET demonstrated significant influence on surgical decision making in adults, with moderate to high sensitivities and PPVs. In children, SPM analysis of PET performed similarly well in the identification of surgical resection areas.

The ultimate reference standard for successful localization is surgical outcome. In adults, the data showed high sensitivity (88% and 89%) for PET with respect to good surgical outcome when MRI is positive. Although the overall sensitivity of PET varied considerably across the studies, PET displayed moderate to high sensitivity in localizing the seizure focus among temporal lobe epilepsy patients (range, 71-89%). Again, this is in line with the previous meta-analysis which showed 86% of patients with good outcome had an ipsilateral PET finding (49). For MRI and EEG, the reported sensitivity (MRI 41-83%; EEG 36-81%) also varied greatly across the studies.[8-16,18,19] Perhaps of greater importance is when PET results were combined with MRI or EEG, the sensitivity of detecting patients with good outcome increased by 8 to 23%.[8-10,13] In children, the addition of PET to magnetoencephalography increased the sensitivity to 95% and decreased the number of false-negative tests for seizure-free outcome.[46] Previous studies have suggested that 55 to 70% of patients undergoing temporal resection achieve a completely seizure-free state, whereas only 30 to 50% of patients undergoing extratemporal resection achieve seizure freedom.[50] The results of the present study suggest that localization is greater in patients with temporal lobe epilepsy, who are more likely to benefit from surgical treatment than in patients with extratemporal lobe epilepsy. It appears that the heterogeneous clinical features of extratemporal (i.e. frontal, insular, occipital, and parietal) epilepsy make accurate localization more difficult. This is a critical issue in children in whom medically refractory extratemporal focal epilepsy is more common in surgical candidates than that of temporal origin. The reverse is true in adult epilepsy surgery candidates. PET findings have been shown to impact patient

Table 7: Impact of ^{18}F-FDG PET on patient management

Study	Study type	Patient population	Category	PET interpretation	Change in surgical management	Comment
Dickson et al, 2013 (abstract)[24]	Retrospective	194 patients with medically refractory focal epilepsy	Adult	SQ	PET findings led directly to surgery in 12 (6%) patients, helped in planning intracranial EEG in 67 (35%) patients, and excluded 24 (12%) from further evaluation	PET benefited 53% of the patients with normal or discordant MRI with clinical/EEG assessments
Popescu et al, 2012 (abstract)[25]	Retrospective	28 with temporal and extratemporal epilepsy	Adult	V, SPM	Both V and SPM were helpful in 48% of the patients to improve guidance of intracranial electrodes placement and in 21% of the patients to avoid stereo-EEG	SPM demonstrated higher sensitivity (74% vs 64%), specificity (93% vs 86%) and accuracy (84% vs 75%) than V in the correct localization of epileptic foci
Uijl et al, 2007[26]	Retrospective	110 TLE patients evaluated for surgery who underwent FDG-PET.	Adult	V, Q	PET findings led clinicians to change the decision regarding surgical candidacy in 78 (71%) patients	The proportions of patients PET accurately predicted to be eligible and ineligible for surgery were 65% and 60%, respectively
Chugani and Conti, 1996[27]	Retrospective	140 infants with spasms	Pediatric	V	With the benefit of PET, the number of cases classified as symptomatic increased from 42 (30%) to 134 (96%). PET showed unifocal (30) and multifocal (62) abnormalities in 95% (92/97) of the cryptogenic cases	None
Ollenberger et al, 2005[28]	Retrospective	118 patients under the age of 14 and had FDG-PET scan for refractory epilepsy	Pediatric	NR	PET had either a minor or a major impact on clinical management in 51% (58/113) of the patients. Surgical candidates—39% surgery excluded and 19% surgery modified. Medical therapy patients—5% surgery excluded and 19% plan modified	PET provided independent information not previously identified with standard diagnostic investigations in 57 (48%) patients
Snead et al, 1996[43]	Retrospective	100 children who underwent evaluation for epilepsy surgery (56, FDG-PET; 44, no FDG-PET)	Pediatric	V	Of the 16 patients with a localizing FDG-PET scan who underwent focal cortical resection or hemispherectomy, 3 avoided chronic invasive recordings because of positive FDG-PET data	There was no significant difference between FDG-PET and no FDG-PET in terms of the number of children who had surgery, the type of procedure, clinical outcome, or whether chronic invasive intracranial monitoring was carried out

NR, not reported; SQ, semiquantitative; TLE, temporal lobe epilepsy.

Table 8: Impact of ^{18}F-FDG PET/MRI coregistration on patient management

Study	Study type	Patient population	Category	PET/MRI interpretation	Change in surgical management	Comment
Salamon et al, 2008[29]	Retrospective	Cohort 1: 45 patients with CD (FDG-PET/MRI coregistration) Cohort 2: 38 patients with CD (before FDG-PET/MRI coregistration)	Adult and pediatric	V	FDG-PET/MRI coregistration enhanced the noninvasive detection of CD in 33% of patients with nonconcordant EEG and neuroimaging findings. Compared with cohort 2 before the regular use of FDG-PET/MRI coregistration, cohort 1 had more patients receiving surgery (+18%), more patients with type I CD on histopathology (60% vs 24%; p = 0.0009), and fewer patients undergoing intracranial electrode studies (2% vs. 21%; p = 0.0060)	Surgical resection guided by FDG-PET/MRI coregistration and electrocorticography resulted in postoperative seizure control in 82% of CD patients
Rubi et al, 2011[30], Rubi Sureda et al, 2010 (abstract)[52]	Retrospective	31 children with refractory epilepsy whose MRI results were nonlesional	Pediatric	V	Of the 21 patients with hypometabolism, 9 (43%) experienced changes in the guided second MRI reading, from nonlesional to subtle lesional	The detection rate of hypometabolism (68%) was the same for both FDG-PET/MRI coregistration and FDG-PET alone
Chassoux et al, 2010[44]	Retrospective	23 patients with histologically proven Taylor-type focal cortical dysplasia and negative MRI	Adult and pediatric	V, SPM	FDG-PET/MRI coregistration detected a partially hypometabolic gyrus in 4 additional cases. In 2 patients, invasive monitoring was avoided because of positive FDG-PET/MRI coregistration results	In all cases, Taylor-type focal cortical dysplasias were located in extratemporal areas and 87% achieved seizure freedom following limited cortical resection

CD, cortical dysplasia.

management by improving the guidance of intracranial electrodes placement, altering the decision to perform surgery or excluding patients from further evaluation.

Because of variable population characteristics (age, types of epilepsy), outcome measurements (inconsistent use of Engel's classification system in reporting surgical outcome), and methods of PET interpretation (V, quantitative, semiquantitative, SPM) among the studies, a meta-analysis was not performed. Instead, a narrative synthesis of the results was presented. The majority of the available studies were retrospective studies with a greater proportion of the evidence in adult patients. This can lead to the introduction of selection bias because only patients proceeding to surgery can be included when surgical outcome was used as a reference standard. Additionally, many of the studies did not report on test specificity, but would be relevant in determining the ability of PET to exclude patients who are unlikely to be amenable to surgery. Although the ideal evidence for evaluating the clinical utility of PET derives from randomized controlled trials, their conduct in this area may not be feasible because of ethical issues.

Currently, FDG PET is widely accepted and recognized as a complementary technique in the presurgical assessment by most epilepsy centres around the world. The combination of imaging findings in relation to each other can enable more accurate localization for surgical resection. Thus, PET can be useful in this setting, particularly in temporal lobe epilepsy patients whose MRI is negative and/or have discordant localizing/lateralizing data from other diagnostic modalities.

Conclusion

The potential benefit of PET in the presurgical evaluation of patients with intractable epilepsy lies in its ability to provide data for localizing the seizure focus and to determine resectability. The evidence from this review proposes that PET is able to provide complementary information that can guide decision-making toward successful surgery. Nonetheless, there is a need for prospective studies to assess the use of PET/MRI and the advantages over standard PET studies.

Disclosures

JGB has received honoraria from and given talks for UCB Canada, EISAI, and Sunovion. The other authors have no disclosures to report.

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