PET Recommendation Report 13

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

The Utility of Positron Emission Tomography in Epilepsy

J.G. Burneo, R. Poon, S. Kellett, S. Houle, and O.C. Snead

Report Date: January 29, 2015

PET Recommendation Report 13 is comprised of 2 sections and is available on the CCO Web site (https://www.cancercare.on.ca)
PEBC PET Recommendation Reports page at:
https://www.cancercare.on.ca/toolbox/qualityguidelines/other-reports/petrecs/
Section 1: Recommendations
Section 2: Evidentiary Base

For further information about this report, please contact:

Dr. Jorge G. Burneo, Associate Professor,
Neurology, Biostatistics and Epidemiology, Western University
339 Windermere Road, Room B10-120
London, Ontario, Canada N6A 5A5
Phone: 519-685-8500 ext. 33464; Fax: 519-663-3498

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Burneo JG, Poon R, Kellett S, Houle S, Snead OC. The utility of positron emission tomography (PET) in epilepsy. Toronto (ON): Cancer Care Ontario; 2015 Jan 29. Program in Evidence-based Care PET Recommendation Report No.: 13.

Journal Citation (Vancouver Style): Burneo JG, Poon R, Kellet S, Snead OC. The utility of positron emission tomography in epilepsy. Can J Neurol Sci. 2015 Nov;42(6):360-71.

PET Recommendation Report 13

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

The Utility of Positron Emission Tomography in Epilepsy

Table of Contents

PET Recommendation Report 13: Section 1

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

The Utility of Positron Emission Tomography in Epilepsy: Recommendations

J.G. Burneo, R. Poon, S. Kellett, S. Houle, and O.C. Snead

Report Date: January 29, 2015

RESEARCH QUESTION

What is the diagnostic accuracy and clinical utility of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) in the presurgical evaluation of adult and pediatric patients with medically intractable epilepsy?

TARGET POPULATION

These recommendations apply to adult and pediatric patients with medically intractable epilepsy being considered for surgery.

INTENDED USERS

- This recommendation report is intended to guide the Ontario PET Steering Committee in their decision making with respect to the development of indications for the use of PET in epilepsy.
- This recommendation report may also be useful to inform clinicians who are seeking information about PET as a presurgical tool in epilepsy.

RECOMMENDATIONS AND KEY EVIDENCE

These recommendations are based on an evidentiary foundation consisting of a systematic review of the literature for the period from 1946 to September 2013.

^{18}F-FDG PET is recommended for the presurgical evaluation of adult and pediatric patients with medically intractable focal or partial epilepsy in the setting of a comprehensive epilepsy surgery program within a Regional Epilepsy Surgery Centre of Excellence.
Key Evidence: Across 13 primary studies, the proportion of adult patients in whom PET correctly localized a seizure focus and had a good surgical outcome ranged from 36% to 89% (1-13). This range improved to 71% to 89% when only considering patients with temporal lobe epilepsy. The corresponding results for pediatric patients were similar to that of the adult population (14,15). When PET results were combined with magnetic resonance imaging (MRI) or electroencephalogram (EEG), the sensitivity of detecting adult patients with good outcome increased by 8% to 23% (1-3,6). In children, the addition of PET to magnetoencephalography

(MEG) increased the sensitivity to 95% and decreased the number of false-negative tests for seizure-free outcome (15).

In surgical decision making, PET accurately predicted surgical candidacy in 68% of the patients and was shown to be the most sensitive test compared with EEG and MRI (16). Another study demonstrated a sensitivity of 60% and a positive predictive value (PPV) of 83% for PET in the identification of all surgical sites. The PPV of PET (94%) was higher for localization of temporal surgical sites (17). In children with intractable epilepsy, statistical parametric mapping (SPM) analysis of PET performed similarly well with a sensitivity of 71% in identifying areas of surgical resection (18).

In terms of impact on patient management, PET findings influenced the clinical decision in 53% to 71% of adult patients and 51% to 95% of pediatric patients (19-23).

Qualifying Statements:

- For localizing epileptic foci or guiding intracranial electrode placement as part of the presurgical evaluation in a Regional Epilepsy Surgery Centre of Excellence, patients with temporal lobe epilepsy may benefit more from PET than patients with extratemporal lobe epilepsy.
- The evidence is suggestive that localization is greater when PET is assessed using SPM and this method may be superior to visual interpretation for particular types of epilepsy. However, defining the exact group of patients for whom PET is likely to provide enhanced localization information based on SPM is beyond the scope of this report.

Due to insufficient evidence, a recommendation cannot be made for or against the use of ^{18}F-FDG PET in the detection of cortical malformations in patients with intractable infantile spasms when MRI or computed tomography (CT) fails to show structural abnormalities.

Key Evidence:
In the diagnostic evaluation of infantile spasms, PET uncovered unifocal or multifocal abnormalities in 95% of cryptogenic cases (22). However, confirmation of focal pathology was not available for those with multifocal abnormalities on PET, which accounted for the majority of children who were reclassified into the symptomatic category.

Qualifying Statements:

- Patients with intractable infantile spasms exhibiting focal metabolic abnormality on PET could be considered for surgery, provided that epileptogenicity of focal malformation is confirmed electrographically during the presurgical evaluation in a Regional Epilepsy Surgery Centre of Excellence. Surgery would not be considered based solely upon a focal area of hypometabolism on PET without other corroborating data.

Due to insufficient evidence, a recommendation cannot be made for or against the use of ^{18}F-FDG PET/MRI coregistration in the presurgical evaluation of patients with medically intractable epilepsy.

Key Evidence:
One study demonstrated that the addition of PET/MRI coregistration to the presurgical evaluation can enhance the detection of cortical dysplasia in patients with epilepsy (24).

However, these findings were based on a relatively small cohort studied retrospectively and provided no information as to whether this technique can be useful for assessing other etiologies in patients being considered for surgery. In another retrospective study involving children with refractory epilepsy, PET/MRI coregistration guided the second MRI interpretation from nonlesional to subtle-lesional in 42% of the cases (25). However, the PET-guided MRI interpretation was performed by only one neuroradiologist and patient outcomes based on these results were not reported.

FUTURE RESEARCH

There is a need for prospective studies to assess the use of PET/MRI and the advantages over standard PET studies.

Funding

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

Updating

All PEBC documents are maintained and updated as described in the PEBC Document Assessment and Review Protocol.

Contact Information

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

PET Recommendation Report 13: Section 2

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

The Utility of Positron Emission Tomography in Epilepsy: Evidentiary Base

J. G. Burneo, R. Poon, S. Kellett, S. Houle, and O.C. Snead

Report Date: January 29, 2015

RESEARCH QUESTION

What is the diagnostic accuracy and clinical utility of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) in the presurgical evaluation of adult and pediatric patients with medically intractable epilepsy?

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures. In Ontario, the prevalence of self-reported epilepsy ranges from 5.0 to 5.2 cases per 1000 population (26). This corresponds to approximately 66,000 Ontario residents diagnosed with this condition (27). For most individuals affected by epilepsy, seizures can be brought under control by drug therapy; however, up to 20% to 30% of patients do not respond to medication and surgical resection of the epileptic focus may be considered (28). The initial stage of the work-up 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 ^{18}F-FDG 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. A number of reports in the past have indicated that PET is safe and may benefit a subset of patients undergoing surgery (29-31), while another report concluded that there is a lack of evidence on the effectiveness and cost-effectiveness of imaging techniques (including PET) in the presurgical work-up to inform clinical practice (32). With new changes in the way care is being delivered to patients in the province of Ontario, only three centres for adults and pediatrics (London Health Sciences Centre, Hospital for Sick Children, and Toronto Western Hospital) will be performing complex epilepsy surgical procedures, including intracranial placement of electrodes. These hospitals are classified as Regional Epilepsy Surgery Centres of Excellence, which have the capacity to provide all appropriate epilepsy-related clinical services to ensure patients are receiving timely and high quality of care (33). Thus, the use of PET would be restricted to these centres.

In response to several requests for PET in the presurgical planning of patients with medically intractable epilepsy through the Ontario PET Access Program, a systematic review of the literature was conducted to provide potential recommendations for the use of ^{18}F-FDG PET in this indication.

METHODS

This recommendation report, produced by the Program in Evidence-Based Care (PEBC) and the Ontario PET Steering Committee of Cancer Care Ontario, was developed through a systematic review of the available evidence. The body of evidence, which forms the basis of the recommendations, was reviewed by two clinical experts in the epilepsy field (JGB, OCS), two methodologists (RP, SK), and one member of the PET Steering Committee (imaging expert in mental illness and addictions) (SH).

This systematic review and companion recommendations are intended to promote evidence-based policy in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC and any associated program is editorially independent from the Ministry.

Literature Search Strategy

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.). See **Appendix I** for the search strategy.

In addition, annual meetings of the American Epilepsy Society (https://www.aesnet.org/meetings_events/annual_meeting_abstracts) were searched up to September 2013 for other relevant abstracts. Likewise, the Canadian Medical Association Infobase (https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx), the National Guidelines Clearinghouse (http://www.guideline.gov/), and the Cochrane Database of Systematic Reviews (http://www.thecochranelibrary.com/view/0/index.html) 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.

Study Selection Criteria

Inclusion Criteria

Fully published reports or abstracts that met the following criteria were selected for inclusion:

- Systematic reviews, randomized controlled trials (RCTs), and prospective or retrospective studies that evaluated the use of ^{18}F-FDG PET in medically intractable epilepsy.

- Studies that included ≥12 patients of any age.
- 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.
- Studies that used a suitable reference standard (intracranial EEG, surgical eligibility, good surgical outcome [Engel class I, II, or III]) when appropriate.

Exclusion Criteria

- Studies of non-^{18}F-FDG PET.
- Non-systematic reviews, letters, editorials, individual case reports, historical articles, or commentaries.
- Reports published in a language other than English.

Synthesizing the Evidence

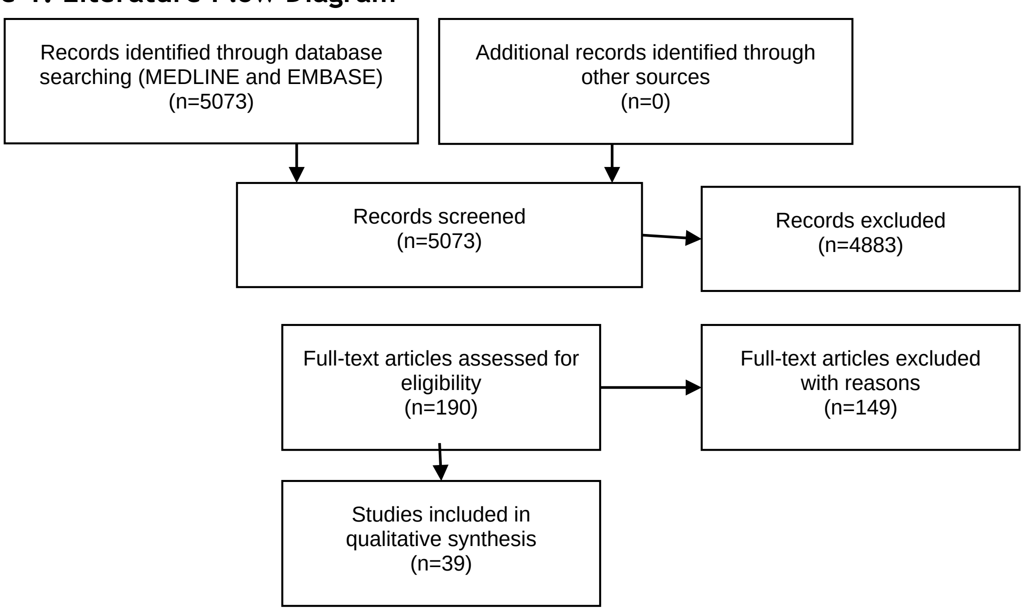
Due to the heterogeneity of the studies in the patient population, study design, outcome measurements, and methods of PET interpretation, the results of the studies included in the systematic review could not be pooled. An assessment of study quality was performed for all fully published reports by one methodologist (RP).

RESULTS

Literature Search 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 RCTs comparing the diagnostic accuracy and clinical utility of ^{18}F-FDG PET with intracranial EEG. However, 36 retrospective studies (1-6,8-14,16-25,34-46) and three prospective studies (7,15,47) were identified to be relevant to this recommendation report (Figure 1). Six of these studies were reported solely in abstract form (11,19,20,37,41,44), while two studies (25,36) had both the full publication and the abstract. The eligible studies were conducted in various contexts but the Working Group believed the outcomes valued in this report would be relevant to the Regional Epilepsy Surgery Centres of Excellence context.

Figure 1: Literature Flow Diagram



Study Design and Quality

For the fully published reports, study quality was assessed using the QUADAS-2 tool (Appendix II). Abstracts were not assessed due to limited reporting of study information. The overall quality varied among the studies but the large majority were judged to have 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) (6,10,13,15,16,40,47), incomplete tests or short follow-up (42), lost to follow up (13), or a definite extratemporal seizure origin (21).

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 (34-40,47). These studies included patients with temporal and/or extratemporal lobe epilepsy. One of the studies (34) reported positive correlation between PET and 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 (39). Overall, the sensitivity at which PET hypometabolism agreed with seizure onset localized by intracranial EEG ranged from 56% to 90%. Among studies that included only temporal lobe epilepsy patients (35,37,47), the sensitivity of PET ranged from 63% to 90% (Appendix III, Table 1).

In pediatric patients, four primary studies were identified that compared PET with intracranial EEG in the localization of seizure foci (18,41-43). In one study (18), 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 (42) 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% across the four studies (Appendix III, Table 2).

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 (16,17,44,45). Two of these evaluated only patients with temporal lobe epilepsy (44,45), while in the other studies, patients with temporal and extratemporal lobe epilepsy were included (16,17). Two studies (16,45) 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 (16). 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) (45). Site of surgery was used as the reference standard in the other two studies (17,44). The abstract by Khan et al (44) reported that 59% of the patients had either lateralizing or localizing PET findings corresponding to the resected seizure focus. The second study (17) reported a similar sensitivity of 60% as well as a PPV of 83% (Appendix III, Table 3). 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 (18) 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 (Appendix III, Table 3). Resection margins were ultimately decided by intracranial EEG.

In 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 (1-6,8-13) and one was part of a prospective observational study (7). 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 (4,11) reported separate sensitivity values for the magnetic resonance (MR)-positive and MR-negative subgroups. The results were similar between the studies for the MR-positive (88% and 89%) and MR-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%. This range improved to 71% to 89% when only considering patients with temporal lobe epilepsy. Furthermore, PET was able to lateralized the seizure focus in 13% to 29% of patients with a good surgical outcome (2,5,6,8,9). In one study (12), 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 (7), 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 (Appendix III, Table 4). These diagnostic values were similar to magnetic source imaging (MSI) (56% sensitivity, 79% specificity, 82% PPV, and 52% NPV).

In Engel class I pediatric patients, one prospective study (15) evaluated the sensitivity (65%), specificity (94%), PPV (68%), and NPV (94%) of PET relative to lobar localization. The corresponding values for magnetoencephalography (MEG) 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 (14), 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 (Appendix III, Table 5).

Impact on Patient Management

^{18}F-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 (21) study, 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 while surgery was ultimately not performed in the other). The abstract by Dickson et al (19) 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 (20), 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 (Appendix III, Table 6).

There were three retrospective studies that provided evidence of a change in clinical management in pediatric patients due to PET. One study (22) 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 (23), 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 (46) compared children who received PET as part of epilepsy surgery evaluation (n=56) to 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. Although of the 16 patients who had focal cortical resection or hemispherectomy, three avoided invasive monitoring due to localizing information provided by PET (Appendix III, Table 6).

^{18}F-FDG PET/MRI coregistration

There were two 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 (24) 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% versus 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 (25,49), PET/MRI coregistration guided the second MRI interpretation from nonlesional to subtle-lesional in 42% of the cases (Appendix III, Table 7).

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 is sufficient for localizing the surgical site and evaluation is based on a consensus of all available diagnostic information. Numerous scenarios arise where 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 (50). Particularly in children, the hospital stay is lengthened due to 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 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. Data from this systematic review showed a 65% 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. While 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% to 89%). Similarly for MRI and EEG, the reported sensitivity (MRI 41% to 83%; EEG 36% to 81%) varied greatly across the studies (1-6,8-10,12,13). 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% (1-3,6). In children, the addition of PET to MEG increased the sensitivity to 95% and decreased the number of false-negative tests for seizure-free outcome (15). Previous studies have suggested that 55% to 70% of patients undergoing temporal resection achieve a completely seizure-free state while only 30% to 50% of patients undergoing extratemporal resection achieve seizure freedom (51). 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 where 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 upon patient management by improving the guidance of intracranial electrodes placement, altering the decision to perform surgery or excluding patients from further evaluation.

Due to 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. While the ideal evidence for evaluating the clinical utility of PET derives from RCTs, 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.

CONCLUSIONS

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.

CONFLICT OF INTEREST

The authors and reviewers reported that they had no conflicts of interest.

ACKNOWLEDGEMENTS

The Working Group would like to thank the following individuals for their assistance in developing this report:

- Ontario PET Steering Committee
- Melissa Brouwers, Sheila McNair, Hans Messersmith for providing feedback on draft versions
- Elizabeth Chan for conducting a data audit
- Sara Miller for copyediting.

REFERENCES

1. Heinz R, Ferris N, Lee EK, Radtke R, Crain B, Hoffman JM, et al. MR and positron emission tomography in the diagnosis of surgically correctable temporal lobe epilepsy. Am J Neuroradiol. 1994;15(7):1341-8.
2. Hong KS, Lee SK, Kim JY, Lee DS, Chung CK. Pre-surgical evaluation and surgical outcome of 41 patients with non-lesional neocortical epilepsy. Seizure. 2002;11(3):184-92.
3. Hwang SI, Kim JH, Park SW, Han MH, Yu IK, Lee SH, et al. Comparative analysis of MR imaging, positron emission tomography, and ictal single-photon emission CT in patients with neocortical epilepsy. Am J Neuroradiol. 2001 May;22(5):937-46.
4. Kassem H, El Shiekh F, Wafaie A, Abdelfattah S, Farghaly H, Afifi L. Presurgical evaluation of refractory temporal lobe epilepsy: Comparison of MR imaging, PET and ictal SPECT in localization of the epileptogenic substrate. Egypt J Radiol Nucl Med. 2013 September;44(3):641-9.
5. Kim DW, Lee SK, Yun CH, Kim KK, Lee DS, Chung CK, et al. Parietal lobe epilepsy: the semiology, yield of diagnostic workup, and surgical outcome. Epilepsia. 2004 June;45(6):641-9.
6. Kim YK, Lee DS, Lee SK, Chung CK, Chung JK, Lee MC. 18F-FDG PET in localization of frontal lobe epilepsy: comparison of visual and SPM analysis. J Nucl Med. 2002 September;43(9):1167-74.
7. Knowlton RC, Elgavish RA, Bartolucci A, Ojha B, Limdi N, Blount J, et al. Functional imaging: II. Prediction of epilepsy surgery outcome. Ann Neurol. 2008 July;64(1):35-41.
8. Kun Lee S, Young Lee S, Kim DW, Soo Lee D, Chung CK. Occipital lobe epilepsy: clinical characteristics, surgical outcome, and role of diagnostic modalities. Epilepsia. 2005 May;46(5):688-95.
9. Lee JJ, Lee SK, Lee Sy, Park KI, Kim DW, Lee DS, et al. Frontal lobe epilepsy: Clinical characteristics, surgical outcomes and diagnostic modalities. Seizure. 2008 September;17(6):514-23.
10. Lee SK, Lee SY, Kim KK, Hong KS, Lee DS, Chung CK. Surgical outcome and prognostic factors of cryptogenic neocortical epilepsy. Ann Neurol. 2005 October;58(4):525-32.
11. Sucak T, Kapucu LO, Capraz I, Akdemir UO, Kurt G, Hirfanoglu T, et al. Comparison of FDG-PET, MRI and EEG findings and surgical outcome in operated lesional and non-lesional temporal lobe epilepsy [abstract]. Eur J Nucl Med Mol Imaging. 2011 October;38:S322-S3.
12. Won HJ, Chang KH, Cheon JE, Kim HD, Lee DS, Han MH, et al. Comparison of MR imaging with PET and ictal SPECT in 118 patients with intractable epilepsy. Am J Neuroradiol. 1999;20(4):593-9.
13. Yun CH, Lee SK, Lee SY, Kim KK, Jeong SW, Chung CK. Prognostic factors in neocortical epilepsy surgery: multivariate analysis. Epilepsia. 2006 March;47(3):574-9. PubMed PMID: 2006114861.
14. Kim JT, Bai SJ, Choi KO, Lee YJ, Park HJ, Kim DS, et al. Comparison of various imaging modalities in localization of epileptogenic lesion using epilepsy surgery outcome in pediatric patients. Seizure. 2009 September;18(7):504-10.
15. Widjaja E, Shammas A, Vali R, Otsubo H, Ochi A, Snead OC, et al. FDG-PET and magnetoencephalography in presurgical workup of children with localization-related nonlesional epilepsy. Epilepsia. 2013 April;54(4):691-9.
16. DellaBadia Jr J, Bell WL, Keyes Jr JW, Mathews VP, Glazier SS. Assessment and cost comparison of sleep-deprived EEG, MRI and PET in the prediction of surgical treatment for epilepsy. Seizure. 2002 July;11(5):303-9.

17. Mastin ST, Drane WE, Gilmore RL, Helveston WR, Quisling RG, Roper SN, et al. Prospective localization of epileptogenic foci: comparison of PET and SPECT with site of surgery and clinical outcome. Radiology. 1996 May;199(2):375-80.
18. Kumar A, Juhasz C, Asano E, Sood S, Muzik O, Chugani HT. Objective detection of epileptic foci by 18F-FDG PET in children undergoing epilepsy surgery. J Nucl Med. 2010 Dec 01;51(12):1901-7.
19. Dickson JC, Rathore C, Ell PJ, Duncan JS. An assessment of the role of FDG PET in the decision making for epilepsy surgery [abstract]. Nucl Med Commun. 2013 April;34(4):368.
20. Popescu CE, Sara R, Mai R, Minniti L, Zanni D, Rossetti C. 18F-FDG PET and SPM analysis in detection of epileptic foci in patients with intractable focal epilepsy [abstract]. Eur J Nucl Med Mol Imaging. 2012 October;39:S257-S8.
21. Uijl SG, Leijten FSS, Arends JBAM, Parra J, Van Huffelen AC, Moons KGM. The added value of [18F]-fluoro-D-deoxyglucose positron emission tomography in screening for temporal lobe epilepsy surgery. Epilepsia. 2007 November;48(11):2121-9.
22. Chugani HT, Conti JR. Etiologic classification of infantile spasms in 140 cases: role of positron emission tomography. J Child Neurol. 1996 January;11(1):44-8.
23. Ollenberger GP, Byrne AJ, Berlangieri SU, Rowe CC, Pathmaraj K, Reutens DC, et al. Assessment of the role of FDG PET in the diagnosis and management of children with refractory epilepsy. Eur J Nucl Med Mol Imaging. 2005 November;32(11):1311-6.
24. Salamon N, Kung J, Shaw SJ, Koo J, Koh S, Wu JY, et al. FDG-PET/MRI coregistration improves detection of cortical dysplasia in patients with epilepsy. Neurology. 2008 Nov 11;71(20):1594-601.
25. Rubi S, Setoain X, Donaire A, Bargallo N, Sanmarti F, Carreno M, et al. Validation of FDG-PET/MRI coregistration in nonlesional refractory childhood epilepsy. Epilepsia. 2011 December;52(12):2216-24.
26. Tellez-Zenteno JF, Pondal-Sordo M, Matijevic S, Wiebe S. National and regional prevalence of self-reported epilepsy in Canada. Epilepsia. 2004;45(12):1623-9.
27. Medical Advisory Secretariat. Functional brain imaging: an evidence-based analysis. Ontario Health Technol Assess Series 2006;6(22).
28. Burch J, Hinde S, Palmer S, Beyer F, Minton J, Marson A, et al. The clinical effectiveness and cost-effectiveness of technologies used to visualise the seizure focus in people with refractory epilepsy being considered for surgery: a systematic review and decision-analytical model. Health Technol Assess. 2012;16(34):1-157.
29. Dussault F-P, Nguyen VH, Rachet F. Positron emission tomography in Quebec [Internet]. AETMIS 01-3 RE. Montreal, Quebec: AETMIS; 2001. Available from: https://www.inesss.qc.ca/fileadmin/doc/AETMIS/Rapports/ImagerieMedicale/2001_03_en.pdf
30. Medical Services Advisory Committee (MSAC). Positron emission tomagraphy [Internet]. Report No. 2822. Canberra, Australia: Commonwealth of Australia; 2000. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/8FD1D98FE64C8A2FCA2575AD0082FD8F/$File/Ref%2002%20-%20Positron%20emission%20tomography%20Report.pdf
31. Medical Services Advisory Committee (MSAC). Positron emission tomagraphy (PET) for epilepsy [Internet]. MSAC reference 26. Canberra, Australia: Commonwealth of Australia; 2004. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/8FD1D98FE64C8A2FCA2575AD0082FD8F/$File/Ref%2026%20-%20Pet%20for%20epilepsy%20Report.pdf
32. Whiting P, Gupta R, Burch J, Mota RE, Wright K, Marson A, et al. A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery. Health Technol Assess 2006;10(4):1-250.

33. Epilepsy Implementation Task Force. Recommendations in the management of epilepsy in adults and children [Internet]. Version 1.0. Critical Care Services Ontario; September 2014. Available from: http://www.epilepsytoronto.org/pub/download.php?file=v3_Recommendations%20in%20the%20Management%20of%20Epilepsy%20in%20Adults%20and%20Children_Sept%2023.pdf
34. Debets RM, van Veelen CW, Maquet P, van Huffelen AC, van Emde Boas W, Sadzot B, et al. Quantitative analysis of 18/FDG-PET in the presurgical evaluation of patients suffering from refractory partial epilepsy. Comparison with CT, MRI, and combined subdural and depth. EEG. Acta neurochir. 1990;50(Suppl):88-94.
35. Delbeke D, Lawrence SK, Abou-Khalil BW, Blumenkopf B, Kessler RM. Postsurgical outcome of patients with uncontrolled complex partial seizures and temporal lobe hypometabolism on 18FDG-positron emission tomography. Invest Radiol. 1996;31(5):261-6.
36. Desai A, Bekelis K, Thadani VM, Roberts DW, Jobst BC, Duhaime AC, et al. Interictal PET and ictal subtraction SPECT: sensitivity in the detection of seizure foci in patients with medically intractable epilepsy. Epilepsia. 2013 Feb;54(2):341-50.
37. Eddeine HS, Chung S. Clinical utility of FDG-PET scan in localizing the epileptogenic focus in non-lesional temporal lobe epilepsy patients [abstract]. Epilepsy Curr. 2012;1).
38. Sadzot B, Debets RMC, Maquet P, Van Veelen CWM, Salmon E, Van Emde Boas W, et al. Regional brain glucose metabolism in patients with complex partial seizures investigated by intracranial EEG. Epilepsy Res. 1992;12(2):121-9.
39. Tatlidil R, Luther S, West A, Jadvar H, Kingman T. Comparison of fluorine-18 deoxyglucose and O-15 water PET in temporal lobe epilepsy. Acta Neurol Belg. 2000 Dec;100(4):214-20.
40. van Huffelen AC, van Isselt JW, van Veelen CW, van Rijk PP, van Bentum AM, Dive D, et al. Identification of the side of epileptic focus with 123I-Iomazenil SPECT. A comparison with 18FDG-PET and ictal EEG findings in patients with medically intractable complex partial seizures. Acta neurochir. 1990;50(Suppl):95-9.
41. Piantino J, Hussein AM. Correlation of pre-surgical PET, MRI and intracranial EEG with pathologic findings in pediatric epilepsy surgery [abstract]. Epilepsy Curr. 2011;1).
42. Seo JH, Holland K, Rose D, Rozhkov L, Fujiwara H, Byars A, et al. Multimodality imaging in the surgical treatment of children with nonlesional epilepsy. Neurology. 2011 Jan 04;76(1):41-8.
43. Seo JH, Noh BH, Lee JS, Kim DS, Lee SK, Kim TS, et al. Outcome of surgical treatment in non-lesional intractable childhood epilepsy. Seizure. 2009 Nov;18(9):625-9.
44. Khan O, Appel S, Dustin I, Reeves-Tyer P, Bagic A, Martinez A, et al. Outcome predictors for temporal lobectomy [abstract]. Epilepsy Curr. 2012;1).
45. Struck AF, Hall LT, Floberg JM, Perlman SB, Dulli DA. Surgical decision making in temporal lobe epilepsy: A comparison of [18F]FDG-PET, MRI, and EEG. Epilepsy Behav. 2011 October;22(2):293-7.
46. Snead 3rd OC, Chen LS, Mitchell WG, Kongelbeck SR, Raffel C, Gilles FH, et al. Usefulness of [18F]fluorodeoxyglucose positron emission tomography in pediatric epilepsy surgery. Pediatr Neurol. 1996 Feb;14(2):98-107.
47. Theodore WH, Sato S, Kufta CV, Gaillard WD, Kelley K. FDG-positron emission tomography and invasive EEG: seizure focus detection and surgical outcome. Epilepsia. 1997;38(1):81-6.
48. Desai A, Thadani VM, Roberts DW, Jobst BC, Duhaime AC, Gilbert K, et al. Sensitivity of interictal PET and ictal subtraction spect in the detection of seizure foci in patients with medically intractable epilepsy [abstract]. Epilepsy Curr. 2012;1).
49. Rubi Sureda S, Setoain X, Donaire A, Bargallo N, Falcon C, Calvo A, et al. Validation of FDG-PET/MRI coregistration in non-lesional refractory childhood epilepsy [abstract]. Eur J Nucl Med Mol Imaging. 2010 October;37:S218.

50. Burneo JB, Steven DA, McLachlan RS, Parrent AG. Morbidity associated with the use of intracranial electrodes for epilepsy surgery. Can J Neurol Sci. 2006 May;33(2):223-7.
51. Tonini C, Beghi E, Berg AT, Bogliun G, Giordano L, Newton RW, et al. Predictors of epilepsy surgery outcome: a meta-analysis. Epilepsy Res. 2004;62(1):75-87.

APPENDIX I. Literature Search Strategy

The search strategy was conducted simultaneously in MEDLINE and EMBASE in OVID on September 25, 2013.

#	Searches	Results
1	exp Epilepsy/	133843
2	epilep$.ti,ab.	101659
3	1 or 2	156634
4	exp Tomography, Emission Computed/	82049
5	(pet or positron emission tomograph$ or positron-emission).ti,ab.	72471
6	or/4-5	109329
7	3 and 6	3594
8	exp Animals/	18070578
9	Humans/ and exp Animals/	13995008
10	8 not 9	4075570
11	7 not 10	3513

APPENDIX II. 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
Comparison between ^{18}F-FDG PET and intracranial EEG in the localization of seizure foci							
Debets et al, 1990 (34)	?	☺	☺	☺	?	☺	☺
Delbeke et al, 1996 (35)	☺	☺	☺	☹	☺	☺	☺
Desai et al, 2013 (36)	☺	?	☹	☺	☺	☺	☺
Sadzot et al, 1992 (38)	?	☺	☹	☺	?	☺	☺
Tatlidil et al, 2000 (39)	☺	☺	☹	☺	☺	☺	☺
Theodore et al, 1997 (47)	☹	☺	☺	☺	☹	☺	☺
Van Huffelen et al, 1990 (40)	☹	☺	☹	☺	☹	☺	☺
Kumar et al, 2010 (18)	☺	☺	☺	☺	☺	☺	☺
Seo et al, 2011 (42)	☹	?	☹	☺	☹	☺	☺
Seo et al, 2009 (43)	☺	?	☺	☺	☺	☺	☺
Diagnostic accuracy of ^{18}F-FDG PET with respect to surgery							
Dellabadia Jr et al, 2001 (16)	☹	☺	☹	☺	☹	☺	☺
Mastin et al, 1996 (17)	☺	☺	☹	☺	☺	☺	☺
Struck et al, 2011 (45)	☺	☺	☹	☹	☺	☺	☺
Diagnostic accuracy of ^{18}F-FDG PET in patients with good surgical outcome							
Heinz et al, 1994 (1)	☺	☺	☹	☺	☺	☺	☺
Hong et al, 2002 (2)	☺	☺	☹	☺	☺	☺	☺
Hwang et al, 2001 (3)	☺	☺	☹	☺	☺	☺	☺
Kassem et al, 2013 (4)	☺	☺	☹	☺	☺	☺	☺
Kim et al, 2004 (5)	☺	☺	☹	☹	☺	☺	☺
Kim et al, 2002 (6)	☹	☺	☹	☺	☹	☺	☺

Knowlton et al, 2008 (7)	☺	☺	☹	☺	☺	☺	☺
Kun Lee et al, 2005 (8)	☺	☺	☹	☺	☺	☺	☺
Lee et al, 2008 (9)	☺	☺	☹	☺	☺	☺	☺
Lee et al, 2005 (10)	☹	☺	☹	☺	☹	☺	☺
Won et al, 1999 (12)	☺	☺	☹	☺	☺	☺	☺
Yun et al, 2006 (13)	☹	☺	☹	☺	☹	☺	☺
Kim et al, 2009 (14)	?	☺	☹	☺	?	☺	☺
Widjaja et al, 2013 (15)	☹	☺	☺	☺	☹	☺	☺
Impact of ^{18}F-FDG PET on patient management							
Uijl et al, 2007 (21)	☹	☺	☹	☺	☹	☺	☺
Chugani & Conti, 1996 (22)	☺	☺	?	?	☺	☺	☺
Ollenberger et al, 2005 (23)	☺	☺	☺	☺	☺	☺	☺
Snead 3rd et al, 1996 (46)	☺	☺	☹	☺	☺	☺	☺
Impact of ^{18}F-FDG PET/MRI coregistration on patient management							
Salamon et al, 2008 (24)	☺	☺	?	?	☺	☺	☺
Rubi et al, 2011 (25)	☺	☺	☹	☺	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

^{18}F-FDG: [18F]2-fluoro-2-deoxy-D-glucose; EEG: electroencephalogram; MRI: magnetic resonance imaging; PET: positron emission tomography

APPENDIX III. Systematic Review Data

Table 1: Comparison between ^{18}F-FDG PET and intracranial EEG in the localization of seizure foci (adult)

Study	Study Type	Study Objective	Patient Population	PET Interpretation	Reference Standard	*Sensitivity Localization	**Sensitivity Lateralization	Clinical Outcome/Comment
Debets et al, 1990 (34)	Retrospective	To establish the potential value of statistical analysis of 18/FDG metabolism in PET as an adjunct /even alternative to depth-EEG in the presurgical evaluation of patients with refractory partial epilepsy.	22 patients with medically intractable complex partial seizures.	V , Q	Intracranial EEG	59% (13/22)	18% (4/22)	Of the 10 patients who had surgery determined by intracranial EEG, 7 remained seizure free.
Delbeke et al, 1996 (35)	Retrospective	To evaluate the relationship between a focus of temporal lobe hypometabolism on 18/FDG-PET and surgical outcome in patients with uncontrolled partial seizures	38 patients with uncontrolled partial seizures.	SQ	Intracranial EEG	86% (19/22)	NR	NR
Desai et al, 2013 (36) and Desai et al, 2012 (abstract) (48)	Retrospective	To determine the relative utility of SPECT and PET in patients with medically refractory epilepsy by comparing these methods to the localization of seizure foci via intracranial EEG.	53 patients with medically refractory epilepsy.	V	Intracranial EEG	56% (25/45)	NR	Of the 33 patients who had resection of a seizure focus identified on intracranial EEG, 21 were seizure free.
Eddeine & Chung, 2012 (abstract) (37)	Retrospective	To compare FDG-PET with intracranial electrodes recording in localizing the epileptogenic focus in MRI-negative TLE patients.	42 TLE patients with normal MRI and sufficient seizures for ictal-focus localization.	NR	Intracranial EEG	90% (9/10)	NR	NR
Sadzot et al, 1992 (38)	Retrospective	To determine whether visual inspection of the metabolic images could be used to better localize the epileptogenic focus.	57 patients with drug-resistant complex partial epilepsy considered for surgery.	V, Q	Intracranial EEG	88% (28/32)	NR	NR
Tatlidil et al, 2000 (39)	Retrospective	To compare FDG-PET and O-15 water PET with regard to lateralization of the seizure focus in	35 patients who underwent an anterior temporal	SQ	Intracranial EEG	NR	77% (10/13)	NR

Study	Study Type	Study Objective	Patient Population	PET Interpretation	Reference Standard	*Sensitivity Localization	**Sensitivity Lateralization	Clinical Outcome/Comment
		patients with complex partial epilepsy.	lobectomy for complex partial seizures.					
Theodore et al, 1997 (47)	Prospective	To study the value of FDG-PET when surface ictal EEG is nonlocalizing.	46 patients with uncontrolled complex partial seizures not localized by ictal surface-sphenoidal video-EEG.	Q	Intracranial EEG	63% (25/40)	NR	Based on intracranial EEG localization, 34 patients had temporal lobectomy and 24 were seizure free.
Van Huffelen et al, 1990 (40)	Retrospective	To compare reduced BZ binding with I-Iomazenil SPECT with reduced glucose metabolism as shown with FDG-PET and ictal EEG monitoring with depth and/or scalp electrodes.	17 patients with medically intractable complex partial seizures and EEG lateralization of the epileptic focus.	Q	Intracranial EEG	88% (7/8)	NR	NR

Abbreviations: BZ: benzodiazepine; EEG: electroencephalogram; ^{18}F-FDG: [18F]2-fluoro-2-deoxy-D-glucose; MRI: magnetic resonance imaging; NR: not reported; PET: positron emission tomography; Q: quantitative; SPECT: single photon emission computed tomography; SQ: semi-quantitative; TLE: temporal lobe epilepsy; V: visual

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

Study	Study Type	Study Objective	Patient Population	PET Interpretation	Reference Standard	*Sensitivity Localization	**Sensitivity Lateralization	Clinical Outcome/Comment
Kumar et al, 2010 (18)	Retrospective	To evaluate and optimize the performance of SPM analysis of FDG-PET scans in pediatric patients.	20 children with intractable focal epilepsy, seizure free after surgery.	V, SPM ($p<0.001$, $p<0.0001$, $p<0.05$)	Intracranial EEG	V: [a]74% SPM: [a]60% - 86%	NR	Other performance parameters: Specificity V: 79% SPM: 77% - 96% PPV V: 57% SPM: 53% - 88% NPV V: 91% SPM: 88% - 94%
Piantino & Hussein, 2011 (abstract) (41)	Retrospective	To determine the correlation between FDG-PET, MRI, intracranial EEG, and pathological findings in the pediatric population.	20 patients with medically refractory epilepsy who underwent surgery.	NR	Intracranial EEG	70% (14/20)	NR	NR
Seo et al, 2011 (42)	Retrospective	To evaluate the localization agreement of individual noninvasive presurgical modalities with intracranial EEG.	14 children with nonlesional intractable focal epilepsy	V, SPM	Intracranial EEG	21% (3/14)	50% (7/14)	Of the 14 patients who had resective surgery guided by intracranial EEG, 7 were seizure free.
Seo et al, 2009 (43)	Retrospective	To investigate seizure outcome following epilepsy surgery in children with medically intractable epilepsy.	27 children with no detectable lesions on MRI and had undergone surgery	NR	Intracranial EEG	78% (21/27)	NR	Of the 27 patients available for follow-up, 18 were seizure free postoperatively.

Abbreviations: EEG: electroencephalogram; ^{18}F-FDG: [18F]2-fluoro-2-deoxy-D-glucose; MRI: magnetic resonance imaging; MSI: Magnetic source imaging; NPV: negative predictive value; NR: not reported; PET: positron emission tomography; PPV: positive predictive value; SPM: statistical parametric mapping; V: visual

*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
[a]Values for numerator and denominator unavailable

Table 3: Diagnostic accuracy of ^{18}F-FDG PET with respect to surgery

Study	Study Type	Study Objective	Patient Population	Category	PET Interpretation	Reference Standard	*Sensitivity	†Specificity	‡PPV	[L]NPV	Clinical Outcome/ Comment
Dellabadia Jr et al, 2002 (16)	Retrospective	To determine whether less-expensive interictal tests could reliably predict the outcome of the comprehensive presurgical evaluation (i.e., surgical treatment or surgical ineligibility).	69 patients admitted for presurgical evaluation.	Adult	V	Surgical candidacy	[a]86%	[a]59%	[a]68%	[a]80%	NR
Khan et al, 2012 (abstract) (44)	Retrospective	To perform a retrospective analysis of presurgical, surgical, and postsurgical data for patients who underwent anterior temporal lobectomy.	99 anterior temporal lobectomy patients	Adult	NR	Resected seizure focus	59% (40/68)	NR	NR	NR	There was a trend for PET toward an association with seizure freedom (p<0.10).
Mastin et al, 1996 (17)	Retrospective	To correlate prospective imaging findings in patients with intractable partial epilepsy with site of surgery and clinical outcome.	35 patients with intractable partial epilepsy who underwent surgery.	Adult	V	Site of surgical resection	60% (15/25)	NR	83% (15/18)	NR	All 15 patients with correct localization of the surgical site had a good outcome (Engel class I-II).
Struck et al, 2011 (45)	Retrospective	To determine the relative contribution of FDG-PET to the surgical decision making for patients with medication-refractory epilepsy and to examine whether PET localization portends a positive	124 patients with medically refractory TLE	Adult	NR	Surgical candidacy	[a]86%	[a]77%	NR	NR	PET was a significant (p=0.02) predictor of postoperative outcome (ILAE class I or ILAE classes II-V).

Study	Study Type	Study Objective	Patient Population	Category	PET Interpretation	Reference Standard	*Sensitivity	†Specificity	‡PPV	└NPV	Clinical Outcome/ Comment
		surgical outcome.									
Kumar et al, 2010 (18)	Retrospective	To evaluate and optimize the performance of SPM analysis of FDG-PET scans in pediatric patients.	20 children with intractable focal epilepsy	Pediatric	V, SPM ($p<0.001$, $p<0.0001$, $p<0.05$)	Site of surgical resection	V: [a]62% SPM: [a]35% - [a]71%	V: [a]89% SPM: [a]86% - [a]98%	V: [a]82% SPM: [a]79% - [a]95%	V: [a]73% SPM: [a]66% - [a]75%	All were seizure free after surgery.

Abbreviations: EEG: electroencephalogram; ^{18}F-FDG: [18F]2-fluoro-2-deoxy-D-glucose; ILAE: International League Against Epilepsy; MRI: magnetic resonance imaging; NPV: negative predictive value; NR: not reported; PET: positron emission tomography; PPV: positive predictive value; Q: quantitative; SPM: statistical parametric mapping; TLE: temporal lobe epilepsy; V: visual

*****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
[a]Values for numerator and denominator unavailable

Table 4: Diagnostic accuracy of ^{18}F-FDG PET in patients with good surgical outcome (adult)

Study	Study Type	Study Objective	Patient Population	PET Interpretation	Reference Standard	*Sensitivity Localization	**Sensitivity Lateralization	[†]Specificity	[‡]PPV	[˪]NPV
Heinz et al, 1994 (1)	Retrospective	To determine the association of an MRI abnormality and a PET abnormality with a good surgical outcome and to determine how MRI and PET findings correlate with histopathological findings in resected tissue.	27 patients with medically intractable TLE.	V	Seizure free or significantly improved*	71% (17/24)	NR	NR	NR	NR
Hong et al, 2002 (2)	Retrospective	To evaluate the surgical outcome and the diagnostic sensitivity of ictal scalp EEG, interictal FDG-PET, and ictal SPECT in nonlesional neocortical epilepsy.	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 (3)	Retrospective	To compare the sensitivities of MRI, PET, and SPECT for presurgical localization of neocortical epileptogenic foci.	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 (4)	Retrospective	To compare the sensitivities of MRI, FDG-PET, and ictal SPECT in localization of the epileptogenic zone in both adult and pediatric patients with refractory TLE.	137 patients who received surgical treatment for intractable epilepsy.	Q	Engel class I-II	MRI-positive: [a]88%	MRI-negative: [a]80%	NR	NR	NR
Kim et al, 2004 (5)	Retrospective	To investigate the clinical features, the prognostic value, and diagnostic sensitivities of various presurgical evaluations and surgical outcomes in patients with parietal lobe epilepsy.	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,	Retrospective	To examine the	29 patients	V, SPM	Engel class I-II	V: 55%	14% (4/29)	NR	NR	NR

Study	Study Type	Study Objective	Patient Population	PET Interpretation	Reference Standard	*Sensitivity Localization	**Sensitivity Lateralization	†Specificity	‡PPV	ᴸNPV
2002 (6)		diagnostic performance of F-FDG PET in FLE.	with FLE.	($p<0.005$, $p<0.001$)		(16/29) SPM: 59% (12/29) - 66% (19/29)				
Knowlton et al, 2008 (7)	Prospective	To determine the value of MSI, FDG-PET, and ictal SPECT in predicting seizure-free outcome following epilepsy surgery.	62 patients with medically intractable partial epilepsy who completed ICEEG and subsequent surgical resection.	V	Engel class I	[a]59%	NR	[a]79%	[a]83%	[a]54%
Kun Lee et al, 2005 (8)	Retrospective	To assess the roles of various diagnostic modalities and the relations between the results obtained by using these diagnostic modalities and surgical outcome.	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 (9)	Retrospective	To assess the role of various diagnostic modalities, including concordances with pre-surgical evaluations.	71 patients with intractable FLE who underwent epilepsy surgery.	V, SPM	Engel class I	36% (12/33)	18% (6/33)	NR	[a]63%	[a]45%
Lee et al, 2005 (10)	Retrospective	To evaluate surgical outcomes and to identify possible prognostic factors.	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) (11)	Retrospective	To evaluate the diagnostic value of FDG-PET, EEG, and MRI in patients with lesional or nonlesional TLE.	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 (12)	Retrospective	To evaluate the concordance rates of ictal video-EEG, MRI, PET, and ictal SPECT to compare the sensitivities of these imaging methods	118 patients who underwent surgery for medically intractable epilepsy.	V	Engel class I-II	NR	86% (68/79)	NR	NR	NR

Study	Study Type	Study Objective	Patient Population	PET Interpretation	Reference Standard	*Sensitivity Localization	**Sensitivity Lateralization	†Specificity	‡PPV	ᴸNPV
		in the lateralization of epileptogenic foci.								
Yun et al, 2006 (13)	Retrospective	To identify favorable prognostic factors for neocortical epilepsy surgery.	193 neocortical epilepsy patients who had undergone focal neocortical resection	V, SPM	Seizure free	63% (67/107)	NR	NR	NR	NR

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

Abbreviations: EEG: electroencephalogram; ^{18}F-FDG: [18F]2-fluoro-2-deoxy-D-glucose; FLE: frontal lobe epilepsy; ICEEG: intracranial EEG; MRI: magnetic resonance imaging; NPV: negative predictive value; NR: not reported; OLE: occipital lobe epilepsy; PET: positron emission tomography; PPV: positive predictive value; Q: quantitative; SPECT: single photon emission computed tomography; SPM: statistical parametric mapping; TLE: temporal lobe epilepsy; V: visual

*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)
ᴸNPV = 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)
[a]Values for numerator and denominator unavailable

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

Study	Study Type	Study Objective	Patient Population	PET Interpretation	Reference Standard	*Sensitivity Localization	**Sensitivity Lateralization	†Specificity	‡PPV	ᴸNPV
Kim et al, 2009 (14)	Retrospective	To evaluate the effectiveness of EEG, MRI, PET, and SISCOM for detecting the seizure foci as verified by surgical outcomes of temporal lobe lesions.	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 (15)	Prospective	To evaluate the sensitivity, specificity, PPV, and NPV of FDG-PET, MEG, FDG-PET + MEG, and FDG-PET/MEG in localization-related nonlesional epilepsy children.	22 children with nonlesional localization-related epilepsy who had surgical resection.	V	Engel class I	[a]65%	NR	[a]94%	[a]68%	[a]94%

Abbreviations: EEG: electroencephalogram; ^{18}F-FDG: [18F]2-fluoro-2-deoxy-D-glucose; MEG: magnetoencephalography; MRI: magnetic resonance imaging; NPV: negative predictive value; NR: not reported; PET: positron emission tomography; PPV: positive predictive value; SISCOM: subtraction of ictal and interictal single photon emission computed tomography coregistered to MRI; V: visual

*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)

ᴸNPV = 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)

[a]Values for numerator and denominator unavailable

Table 6: Impact of ^{18}F-FDG PET on patient management

Study	Study Type	Study Objective	Patient Population	Category	PET Interpretation	Change in Surgical Management	Comment
Dickson et al, 2013 (abstract) (19)	Retrospective	To determine the benefit of FDG-PET in surgical decision making for patients with nonlocalizing or discordant information on noninvasive evaluation (clinical, EEG, MRI).	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) (20)	Retrospective	To evaluate and compare the performance of both visual and voxel-based analysis of FDG-PET and to study their role in surgical management of intractable focal epilepsy.	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 (21)	Retrospective	To determine the clinical or added value of FDG-PET on the decision-making process regarding TLE surgery in the setting of a tertiary referral centre.	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 & Conti, 1996 (22)	Retrospective	To determine the effectiveness of FDG-PET in classifying symptomatic infantile spasms and evaluate its incremental value over conventional diagnostic methods.	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 (23)	Retrospective	To examine the impact of FDG-PET on deciding whether a child was a candidate for epilepsy surgery from the managing clinician's perspective.	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 3rd et al, 1996 (46)	Retrospective	To determine the usefulness of FDG-PET in selecting children with medically intractable epilepsy for surgical treatment.	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 due to FDG-PET	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

Study	Study Type	Study Objective	Patient Population	Category	PET Interpretation	Change in Surgical Management	Comment
						data.	intracranial monitoring was carried out.

Abbreviations: EEG: electroencephalogram; ^{18}F-FDG: [18F]2-fluoro-2-deoxy-D-glucose; MRI: magnetic resonance imaging; PET: positron emission tomography; NR: not reported; Q: quantitative; SPM: statistical parametric mapping; SQ: semi-quantitative; TLE: temporal lobe epilepsy; V: visual; vs.: versus

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

Study	Study Type	Study Objective	Patient Population	Category	PET/MRI Interpretation	Change in Surgical Management	Comment
Salamon et al, 2008 (24)	Retrospective	To determine whether FDG-PET/MRI coregistration enhanced the recognition of CD in the evaluation of patients with therapy-resistant epilepsy.	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 (25) and Rubi Sureda et al, 2010 (abstract) (49)	Retrospective	To validate the use of interictal FDG-PET/MRI in detecting cortical lesions in MRI nonlesional childhood epilepsy.	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.

Abbreviations: CD: cortical dysplasia; EEG: electroencephalogram; ^{18}F-FDG: [18F]2-fluoro-2-deoxy-D-glucose; MRI: magnetic resonance imaging; PET: positron emission tomography; V: visual; vs.: versus