TITLE:   Positron Emission Tomography for Epilepsy: Clinical Effectiveness and Guidelines

DATE:  15 June 2010

CONTEXT AND POLICY ISSUES:

Epilepsy is a chronic neurological disorder and 70% of the cases can be controlled by medication. The remaining 30% develop intractable seizures and cannot be controlled by medication alone. In those cases, epilepsy surgery of the brain is considered for therapeutic purposes or to obtain a cure. The success of surgery relies on the localization of the epileptogenic focus that causes seizures. Several diagnostic modalities are available to localize the epileptogenic tissue. They are classified as anatomic (structural and chemical) and functional.

Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) are anatomic diagnostic modalities. MRI is the technique of choice for suspected structural abnormalities. In most cases, the localization of epileptogenic foci relies on functional studies in addition to MRI. The functional diagnostic modalities include scalp electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), single photon emission computed tomography (SPECT), subtraction ictal SPECT coregistered to MRI (SISCOM), functional MRI, optical recording of intrinsic signals (ORIS), and invasive EEG. Invasive EEG is currently regarded as gold standard for identifying epileptic foci.

PET is a neuroimaging diagnostic modality that involves the use of a short-lived radioactive tracer isotope injected into blood circulation. The most common used tracer is $^{18}$F fluorodeoxyglucose (FDG). FDG is a glucose analog that is readily taken up by metabolically active cells. FDG-PET has been used in preoperative evaluation of epilepsy, particularly in cases of temporal lobe epilepsy. Other radionuclides include $^{[11]}$C- or $^{[18]}$F-flumazenil, $^{[13]}$carfentanil, and $^{[14]}$methyl-L-tryptophan.

It is unclear to what extent PET contributes additional value in the decision making process for epilepsy surgery, and how significant PET results are associated with post-surgical outcomes. The report reviews the current evidence for the clinical effectiveness and guidelines for the use of PET in the preoperative evaluation and management of patients with epilepsy.
RESEARCH QUESTIONS:

1. What is the clinical effectiveness of the use of positron emission tomography for the management of epilepsy?

2. What are the guidelines for use of positron emission tomography for the management of epilepsy?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 5, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and May 17, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and guidelines.

SUMMARY OF FINDINGS:

Two health technology assessments (HTA),5,6 one systematic review,7 and 11 observational studies8-18 not included in the HTAs and systematic review, and three guidelines6,19,20 were identified. No randomized controlled trials were identified.

Health technology assessments

Of the two identified HTAs,5,6 the first one5 dealt with different neuroimaging techniques while the second one6 specifically assessed PET for epilepsy and developed recommendations, which are reported in the guideline sections.

Whiting et al., 20065 conducted a systematic review of the effectiveness and cost-effectiveness of different diagnostic tests to detect the seizure focus in patients with refractory epilepsy being considered for surgery. Seventy two studies with a total of 3156 patients (range from 20 to 177) were included. The mean age ranged from 3 months to 72 years. Of those studies, 18 investigated PET. Only the clinical effectiveness of PET is summarized here. The included patients had temporal and/or non-temporal lobe epilepsy. The tracers used varied between studies.

PET correctly localized the seizure focus in 29% to 92% of patients. PET failed to localize a seizure focus in 0 to 56% of patients. The proportion of patients in whom PET partially localized the seizure focus ranged from 0 to 62%. There was considerable heterogeneity between studies in all localization categories.

Similar findings were found between PET and ictal SPECT in the proportion of scans of the localization categories (7 studies). Compared with interictal SPECT, four studies reported that PET scans more correctly localized the seizure focus. Compared with routine MRI, five studies reported that PET correctly localized a greater proportion of seizure foci than MRI, while two studies reported otherwise. Compared with MRS, two studies showed neither technique
appeared to be superior to the other. One study reported that PET was superior to computed tomography (CT) for localizing seizure foci.

Three studies reported the association of PET results with outcomes following surgery. The first study, using univariate analysis, showed that only a positive PET scan of the temporal pole region showed a significant association with the seizure-free outcome (p=0.005) as opposed to the extratemporal region. The second study, using multiple regression analysis, found that PET had a significant association with positive outcomes (Engel I and II combined) (p=0.007), whereas MRI had only a borderline significant association (p=0.07). Engel class I indicates seizure-free and Engel class II indicates greater than 90% reduction in seizure frequency. The third study, using X² analysis, found that PET did not have a significant association with seizure outcomes. This study also found that PET did not differ significantly from MRI in the prediction of surgical outcome.

Several limitations were identified by the authors of the HTA. They stated that the identified studies were non-RCTs and of poor quality or poorly reported. The study designs, patient characteristics, outcome measures, and reference standards varied between studies. The data did not fit the 2 x 2 table of test performance, and hence standard measures such as sensitivity, specificity, likelihood ratios, and predictive values could not be calculated. Pooling of data was therefore not carried out.

Due to the limitations of the identified studies, the authors concluded that there was insufficient evidence regarding the effectiveness of imaging techniques including PET in the preoperative evaluation for epilepsy surgery.

The Medical Services Advisory Committee (MSAC) of Australia reviewed the use of PET with the radionuclide FDG for patients with epilepsy. Based on the eligibility criteria, 12 studies (case series) were included in the review. The safety of PET was reviewed and with respect to radiopharmaceutical risks, none of the studies reported any adverse events associated with the radiotracers used with PET.

For the assessment of effectiveness of PET, evidence from case series (level IV) showed that the median percentage of localization provided by PET was 70% (range 39-100%). The median proportion of patients having positive post-surgical outcomes (seizure-free) after a PET scan was 67% (range 29% -100%). The authors stated that the accuracy of PET could not be estimated due to the fact that the majority of the studies did not use a reference standard to determine whether the localization was “correct”. One study found that PET was promising in the clinical management of epilepsy.

Several limitations were identified by the authors. First, the accuracy might be overestimated due to the fact that only patients with a positive PET result are more likely to undergo surgery, and therefore the reported correct localization will be overestimated. Second, test specificity or negative predictive value was not been described due to the missing true negative values. Third, the accuracy results may not widely transferable due to the inclusion of unrepresentative sample of patients (spectrum bias).

The expert panel concluded that PET is safe and may provide extra localization information in patients with refractory epilepsy, in whom MRI and EEG fail to localize a seizure focus, and some of these patients will have good outcome after surgery.
Systematic reviews and meta-analyses

Willmann et al., 2007\(^7\) conducted a meta-analysis to determine the diagnostic value of PET in the presurgical evaluation of patients with temporal lobe epilepsy (TLE). Forty six studies from January 1992 to June 2006 were included. The length of follow-up after surgery varied from 3 months to 144 months. PET was used as confirmatory test in the included studies. Meta-analysis of PET was performed on 153 TLE patients, all of which had undergone ictal scalp EEG and MRI. Forty one patients had recording of invasive EEG in addition to other diagnostic tests.

The agreement between PET and ictal scalp EEG, PET and MRI, and PET and invasive EEG was 75.2% (115/153), 68.6% (105/153), and 46.3% (19/41), respectively. The concordance to the side of surgery for ictal EEG, MRI, PET, and invasive EEG was 86.9% (133/153), 77.1% (118/153), 83.0% (127/153), and 100% (41/41), indicating that all diagnostic tests correlated well with the final defined surgical side. The positive predictive values (PPV) of each diagnostic test performing alone were similar and in the range of 70% to 80%. When MRI or EEG or even both were non-concordant with the reference method, the overall PPV of PET was 77.5%. However, the odds ratio was 1.292 with wide confidence interval [0.282-5.908], indicating a non-significant difference.

Limitations of the identified studies reported by the systematic review authors included small number of patients, substantial heterogeneity and discrepancies in the methodologies and scopes, and lack of patients' information. All studies were non-RCTs.

The authors concluded that PET may be a good diagnostic test to evaluate TLE for surgery, although the actual diagnostic added value remains unclear. They also stated that PET does not add any additional value in patients with their seizure foci localized by MRI or EEG.

Observational studies

Eleven studies\(^8\)-\(^\text{18}\) of PET in patients with epilepsy were identified. All studies were of retrospective design. Of these studies, seven reported localization and outcomes, three reported localization only, and one was a survey. The number of participants ranged between 21 and 469. Summary of the characteristics and results of the studies are shown in Appendix 1.

Kim et al, 2009\(^8\) determined the accuracy of different imaging modalities (EEG, MRI, PET, and SISCOM) in identifying epileptogenic zones in pediatric patients (N=42) who successfully received epilepsy surgery. The results showed that localizing power of MRI was highly accurate in all cases. PET results were more reliable in temporal lobe lesions while SISCOM data was useful in extratemporal locations. It was concluded that, in cases of conflicting pre-surgical results, MRI and PET are advised for temporal cases, while MRI and SISCOM are advised for extratemporal cases. This study was limited in that most of the extratemporal cases were frontal lobe seizures, and the localizing power of the imaging modalities was not known in patients with less favorable surgical outcomes.

Seo et al, 2009\(^9\) reported their experience with a series of pediatric patients (N=27) with epilepsy surgery for non-lesional intractable epilepsy. Only patients with normal MRI were included, and all patients had undergone EEG, PET, and SPECT. Of the 27 patients available
for follow-up (mean post-operative follow-up: 4.3 years, range: 2.2 - 9 years), 82% of patients had favorable outcome in Engel class I or II (67% class I and 15% class II). EEG revealed abnormalities in all patients, while 67% of patients showed focal localization features on ictal SPECT, and 78% showed abnormal PET. It was concluded that in children with intractable epilepsy and normal MRI, epileptic surgery is considered when cortical abnormalities can be identified from other diagnostic tests.

Boling et al, 2008 evaluated preoperative FDG-PET activity in temporal lobe structures and contrasted with MRI for usefulness in identifying mesial temporal lobe epilepsy in adult patients (N=28). All patients underwent MRI and FDG-PET before surgery. The results showed that MRI or FDG-PET alone was not reliable to identify mesial temporal lobe epilepsy. However, combination of MRI and PET correctly identified all patients with and without mesial temporal lobe epilepsy. It was concluded that combination of PET imaging and MRI visual inspection was superior in the recognition of mesial temporal lobe epilepsy.

Buch et al, 2008 compared the results of 21 patients' ratio-images of SPECT/PET and PET readings to the corresponding sites of successful surgical reaction. All patients underwent PET and SPECT. Statistical parametric mapping was used to create SPECT/PET ratio-images. Localization was determined by comparing the hemispheric location of the visualized areas to the sites of surgical resection. Patients’ information was not reported. The results showed that PET and ratio SPECT/PET had similar sensitivity (68.0% versus 70.8%) and specificity (96.2% versus 96.0%). However, hemispheric localization of PET was 69.6% and of ratio SPECT/PET was 82.6%. The authors concluded that the ratio image of SPECT/PET may be a valuable diagnostic tool in the hemispheric localization to enhance the use of PET.

Knowlton et al, 2008 determined the relative predictive value of magnetic source imaging (MSI), FDG-PET, and SPECT to replace or supplement information provided by intracranial EEG in patients with epilepsy. Patients (N=72) completing intracranial EEG monitoring underwent MSI and PET. SPECT was obtained when indicated. Patients’ information was not reported. The results showed that MSI had higher sensitivity and specificity values than PET or SPECT, and MSI had greatest level of concordance with intracranial EEG. The specificity was increased with the combination of PET and MSI or SPECT and MSI. It was concluded that positive MSI has a high predictive value for seizure localized with intracranial EEG, and combination of PET and MSI or SPECT and MSI increases diagnostic values.

Knowlton et al, 2008 published another study of results of the same cohort of patients who underwent epilepsy surgery after being preoperatively evaluated by intracranial EEG, MSI, PET, and SPECT. After surgery, 61% of patients were seizure-free (Engel class I). The localization rates of MSI, PET, and SPECT were 50%, 47% and 41%, respectively. The odds ratio (OR) for MSI prediction of seizure-free outcome was 4.4 (p=0.01). In cases when both PET and MSI was used, the adjusted OR for PET was 7.1 (p<0.01) and for MSI was 6.4 (p=0.01). In cases when MSI, PET, and SPECT were used, the OR for SPECT was highest. It was concluded that conclusively positive MSI, PET, or SPECT can guide decisions for successful surgery in patients with epilepsy who typically require intracranial EEG.

Lee et al, 2008 assessed the role of various modalities (MRI, EEG, PET, and SPECT) in the presurgical evaluation of patients with intractable frontal lobe epilepsy (N=71), who underwent surgery and whose outcomes were followed up for more than 2 years. The results showed that
the predictive values (both negative and positive) were comparable between diagnostic modalities. The diagnostic accuracy of PET and SPECT had no significant relationship with surgical outcome, whereas MRI was statistically significantly associated with surgical outcomes (P=0.029). It was concluded that only MRI can predict surgical outcome, although various methods can be useful in the diagnosis of frontal lobe epilepsy.

Salamon et al, 2008\(^{15}\) compared the diagnostic and surgical results of a 2004-2007 cohort in which FDG-PET/MRI coregistration studies were a routine part of presurgical evaluation to a 2000-2003 cohort in which such combined technique was not available. Epilepsy patients (N=45) with cortical dysplasia were included. It was found that combined PET/MRI detected more cortical dysplasia patients and fewer cases required intracranial EEG. More 2004-2007 patients had surgery compared to 2000-2003 patients, and 82\% of 2004-2007 patients were seizure-free after surgery. It was concluded that PET/MRI coregistration enhanced the identification and successful surgical treatment of patients with cortical dysplasia, especially those with nonconcordant results and those with normal MRI scans.

Kurian et al, 2007\(^{16}\) determined the extent to which PET, SPECT, and its coregistration with MRI contributed to correct localization of epileptogenic focus, surgical intervention, and to the post-surgical outcome in pediatric patients with drug-resistant epilepsy (N=50). All patients underwent EEG, MRI, PET, and SPECT. Surgical decision was based on combined results of EEG and MRI. Intracranial EEG was considered when discordant results occurred. Mean follow-up after surgery was 21 months (range 12-48 months). The results showed that localization concordant to the operation site for MRI, PET, and SPECT was 82\%, 78\%, and 76\%, respectively. Localization with more imaging modalities yielded higher benefit from surgical treatment compared to single modality. The authors concluded that the combined use of multiple imaging modalities in the pre-surgical evaluation of pediatric epilepsy is worthwhile and better for postoperative seizure control, especially when EEG and MRI alone are unable to localize a seizure focus.

Uijl et al, 2007\(^{17}\) assessed the added value of FDG-PET in the decision-making for temporal lobe epilepsy surgery in relation to MRI or EEG. Patients (N=469) underwent FDG-PET, MRI, or EEG, alone or in combination to determine whether to perform surgery. It was found that 23\% of patients underwent PET, and 71\% of those patients with PET findings led clinicians to change their decision based on MRI and EEG findings. FDG-PET was most useful when previous MRI was normal, or when EEG results were not consistent with MRI. Combination with PET with MRI or PET with EEG improved positive and negative predictive values. The authors concluded that FDG-PET added more diagnostic value in screening for temporal lobe epilepsy surgery, especially when MRI or EEG monitoring are non-localizing.

Ollenberger et al, 2005\(^{18}\) performed a survey to examine the influence of FDG-PET in the decision-making for epilepsy surgery in pediatric patients with refractory epilepsy (N=118). FDG-PET scan results were compared with MRI, EEG, and SPECT results. The survey found that FDG-PET provided additional information to other investigations regarding epileptogenic sites in 77\% of patients. Managing physicians indicated that PET scan results changed clinical management in 51\% of patients, mainly those considered for surgery. The authors concluded that FDG-PET has a definite role in the assessment of pediatric patients with refractory epilepsy who are being considered for surgery.
Guidelines and recommendations

Three relevant guidelines\textsuperscript{6,19,20} were identified.

The Medical Services Advisory Committee (MSAC)\textsuperscript{6} of Australia reviewed the use of PET as diagnostic technology for the indication of epilepsy. Based on the evidence identified in the literature and other information sources including clinical expertise, MSAC came up with recommendations, taking into account of safety, effectiveness, cost-effectiveness, and issues of access and equity.

Level IV evidence (case series) showed that PET is safe, provides additional information for potential good post-surgical outcomes, and may be cost-effective in the long term. MSAC recommends that PET should be supported by public funding. The recommendation was accepted by the Minister of Health and Aging of Australia in 2005.

The American College of Radiology Committee on Appropriate Criteria, Expert Panel on Neurological Imaging\textsuperscript{19,21} reviewed and updated the guidelines on the appropriateness of initial radiologic examinations for adult patients with epilepsy. The interventions and practices considered included MRI, magnetic resonance angiography (MRA), functional MRI, SPECT, FDG-PET, MSI, CT. Evidence was systematically reviewed and Expert Consensus (Delphi) was used to formulate the recommendations. The rating scheme to assess the quality and strength of the evidence was not given. The rating scale of the recommendations was from 1 (least appropriate) to 9 (most appropriate). Five variants of epilepsy were classified. MRI was rated 8 in all variants with no concern on the relative radiation level (RRL).

- Variant 1: Chronic epilepsy, poor therapeutic response (surgery candidate). FDG-PET was rated 7 with high RRL. It is considered helpful in preoperative evaluation.
- Variant 2: New onset of seizure (ethy alcohol, and/or drug related). FDG-PET was rated 2 with high RRL.
- Variant 3: New onset seizure (Aged 18-40 years). FDG-PET was rated 4 with high RRL.
- Variant 4: New onset seizure (Older than age 40 years). FDG-PET was rated 4 with high RRL.
- Variant 5: New onset seizure (Focal neurological deficit). FDG-PET was rated 3 with high RRL.

The American College of Radiology Committee on Appropriate Criteria, Expert Panel on Neurological Imaging\textsuperscript{20,22} reviewed and updated the guidelines on the appropriateness of initial radiologic examinations for pediatric patients with epilepsy. The interventions and practices considered included MRI, CT, ultrasound (US), FDG-PET, and SPECT. Evidence was systematically reviewed and Expert Consensus (Delphi) was used to formulate the recommendations. The rating scheme to assess the quality and strength of the evidence was not stated. The rating scale of the recommendations was from 1 (least appropriate) to 9 (most appropriate). Five variants of epilepsy were classified. Seven variants of epilepsy were classified. The following rating of PET was compared with the modality having highest rate.

- Variant 1: Neonatal seizures. FDG-PET was rated 1, while US was rated 8.
- Variant 2: Partial seizures. FDG-PET was rated 5, while MRI (without contrast) was rated 8.
- Variant 3: Post traumatic seizures. FDG-PET was rated 1, while CT (without contrast) was rated 9.
- Variant 4: First generalized seizure (neurologically normal). FDG-PET was rated 1, while MRI (without contrast) was rated 5.
- Variant 5: Generalized seizure (neurologically abnormal). FDG-PET was rated 2, while MRI (without contrast) was rated 8.
- Variant 6: Intractable or refractory seizures. FDG-PET was rated 6, while MRI (without contrast) was rated 9.
- Variant 7: Febrile seizures: FDG-PET was rated 6, while MRI (without contrast) was rated 2.

Limitations

No controlled studies were identified on the use of PET to manage epilepsy. Most identified studies were of retrospective design. The calculations of diagnostic values were often not correctly estimated. Sensitivity and specificity was calculated using only patients with successful surgeries, while patients with unsuccessful surgeries were usually not included. There were substantial heterogeneities among studies with respect to objectives, scopes, type of tracers used, type of epilepsy, comparators, and reference standard. Pooling of data was therefore not possible.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The limited information identified does not appear to support the use of PET alone in the evaluation of epilepsy before surgery and did not indicate a significant association of PET with favorable outcomes after surgery. One HTA in 2006 concluded that effectiveness of PET in the preoperative evaluation of epilepsy surgery is inconclusive due to limitations of the included studies. Another HTA of the same year stated that PET may provide extra localization information in patients whose MRI or EEG results failed to localize a seizure focus. The identified systematic review also found that PET did not add any additional value in patients with their seizure focus localized by MRI or EEG, although it may be a good diagnostic test to evaluate temporal lobe epilepsy for surgery. Results from the identified observational studies suggest that the combination use of PET and other imaging modalities such as MRI or SPECT during preoperative evaluation increases the likelihood of localization and yields favorable outcomes after surgery, especially when MRI or EEG results are normal. The American College of Radiology guidelines have rated their recommendations for the use of PET in the preoperative evaluation of different variants of epilepsy in both adult and pediatric patients. The Australian guidelines recommended that PET for the indication of epilepsy should be supported by public funding, based on level IV evidence. One study showed that FDG-PET had an impact on changing clinical management in patients considered for epilepsy surgery. Taken together, evidence from uncontrolled studies showed that PET could be a valuable tool for preoperative evaluation of epilepsy surgery, and that its use in conjunction with other imaging modalities may be worthwhile. The poor quality of the evidence may be a consideration for decision-making.

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REFERENCES:


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<th>Study</th>
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<tr>
<td>Kim et al, 2009</td>
<td>Localization and outcomes</td>
<td>42</td>
<td>Pediatric pts admitted to Severance Children’s Hospital, South Korea, between October 2003 and April 2008, and received epilepsy surgery (focal lobectomies or corticosectomies). Selected pts were divided into temporal and extratemporal lesion groups.</td>
<td>Retrospective. EEG and MRI were performed in all pts. FDG-PET was performed in 19 pts with extratemporal lesion and 22 pts with temporal lobe lesions. SISCOM was performed in 13 extratemporal and 12 temporal cases.</td>
<td>31M, 11F 23 temporal lobe lesions 19 extratemporal lesions Mean age at surgery 16.42 yrs (range 1.34-19.67 yrs) Mean duration of follow-up since surgery 2.15 yrs (range 0.59-5.05 yrs)</td>
<td>EEG, MRI, SISCOM</td>
<td>Surgical outcome</td>
<td>EEG: concordance rate 100%, both temporally and extratemporally. 88% localization and 12% lateralization. MRI: Temporally, concordance rate 91.3%, with 82.6% localization and 8.7% discordance. Extratemporally, concordance rate 84.2%, with localization in all concordance cases. 15.8% discordant. FDG-PET: Temporally, concordance rate 95.5%, with 72.7% localization and 4.5% discordance. Extratemporally, concordance rate 68.4%, with 63.2% localization and 31.6% discordance SISCOM: Temporally, concordance rate 100%, with only 66.7%</td>
<td>Localization power of MRI is highly accurate. FDG-PET was reliable for temporal epileptic area, but its efficacy was lower for extratemporal cases. SISCOM was more efficacious for extratemporal than temporal cases. In cases of conflict pre-surgical results, MRI and PET are advised for temporal cases, while MRI and SISCOM for extratemporal cases.</td>
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<td>Seo et al, 2009&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Localization and outcomes</td>
<td>27</td>
<td>Pts with retractable childhood epilepsy who received surgery between 1999 and 2006 at Sang-gye Paik Hospital and Severance Children’s Hospital, South Korea. Only pts with normal MRI was included.</td>
<td>Retrospective. All pts underwent EEG, PET, and SPECT.</td>
<td>16M, 11F Mean age at surgery 1.8 yrs (range 2-16 yrs) Mean of postoperative follow-up 4.3 yrs (2.2-9 yrs)</td>
<td>EEG, SPECT</td>
<td>Surgical outcome</td>
<td>Localization. Extratemporally, concordance rate 92.3%, with 84.6% localization and 7.7% discordance. Hippocampal sclerosis was in most temporal cases and cortical dysplasia in extratemporal cases.</td>
<td>In children with intractable epilepsy and normal MRI, epileptic surgery is considered when cortical abnormalities can be identified from other diagnostic tests.</td>
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<td>Boling et al, 2008&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Localization and outcomes</td>
<td>28</td>
<td>Consecutive pts with mesial temporal lobe epilepsy</td>
<td>Retrospective. All pts underwent MRI and FDG-PET</td>
<td>11M, 17F Mean age 35 yrs (range 17-57 yrs)</td>
<td>MRI</td>
<td>Surgical outcome</td>
<td>MRI and PET were comparable (p=0.73). MRI or FDG-PET</td>
<td>Combination of PET imaging and MRI visual</td>
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<td>Buch et al, 2008^11</td>
<td>Localization</td>
<td>21</td>
<td>Pts with refractory epilepsy who received evaluation and subsequent surgical resection at the Yale Epilepsy program, USA</td>
<td>Retrospective. All pts underwent PET and SPECT. Statistical parametric mapping was used to create SPECT/PET ratio-images</td>
<td>8M, 13F Other pts data: not reported</td>
<td>Ratio-image of SPECT/PET</td>
<td>Localization was determined by comparing the hemispheric location of the visualized areas to the sites of surgical resection</td>
<td>PET and ratio SPECT/PET had similar sensitivity (68.0% vs. 70.8%) and specificity (96.2% vs. 96.0%) Hemispheric localization by PET was 69.6% and by ratio SPECT/PET 82.6%</td>
<td>The ratio image of SPECT/PET may be a valuable diagnostic tool in the hemispheric localization to enhance the use of PET.</td>
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<td>Knowlton et al, 2008^12</td>
<td>Localization</td>
<td>72</td>
<td>Pts completing intracranial EEG monitoring at the UAB Epilepsy Center and the Children Hospital of Alabama between August 2001 and March 2006 Pts required intracranial EEG</td>
<td>Retrospective All pts underwent MSI. PET and SPECT were obtained when indicated</td>
<td>Pts information: not reported</td>
<td>Intracranial EEG</td>
<td>Not reported</td>
<td>Sensitivity: MSI (58-64%), PET (24-40%), SPECT (40-50%) Specificity: MSI (78-88%), PET (53-63%), SPECT (40-50%). MSI had higher diagnostic values than PET or SPECT. MSI + PET or MSI</td>
<td>Positive MSI has a high predictive value for seizure localized with intracranial EEG. Combination of PET and MSI or SPECT and MSI increases</td>
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<td>Knowlton et al, 2008¹³</td>
<td>Localization and outcomes</td>
<td>62</td>
<td>Pts with intractable partial epilepsy underwent epilepsy surgery (same cohort of pts in Knowlton et al, 2008¹²)</td>
<td>Retrospective</td>
<td>Pts information: not reported</td>
<td>Intracranial EEG</td>
<td>Surgical outcome</td>
<td>61% of total were seizure-free (Engel class I) Localization: MSI (50%), PET (47%), SPECT (41%) OR for prediction of seizure-free outcome: • MSI: 4.4 (p=0.01) • When PET + MSI was used, the OR for PET was 7.1 (p&lt;0.01) and the OR for MSI was 6.4 (p=0.01)</td>
<td>Conclusively positive MSI, PET, or SPECT can guide the decision for successful surgery to pts who typically require intracranial EEG</td>
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<tr>
<td>Lee et al, 2008¹⁴</td>
<td>Localization and outcomes</td>
<td>71</td>
<td>Consecutive pts with intractable frontal lobe epilepsy underwent surgery and whose outcomes were followed up for more than 2 yrs.</td>
<td>Retrospective</td>
<td>44M, 27F Mean age at surgery 25.5 yrs</td>
<td>MRI, EEG, SPECT</td>
<td>Surgical outcome</td>
<td>PPV for interictal EEG (62.5%), ictal EEG (56.4%), MRI (73.9%), PET (63.2%), and ictal SPECT (63.6%) NPV for interictal EEG (46.0%), ictal EEG (44.4%), MRI</td>
<td>Only MRI can predict surgical outcome, although various methods can be useful in the diagnosis of frontal lobe epilepsy</td>
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<td>Study</td>
<td>Type of study</td>
<td>N</td>
<td>Patient source and selection</td>
<td>Study design</td>
<td>Patient characteristics</td>
<td>Comparator</td>
<td>Reference standard</td>
<td>Results</td>
<td>Conclusion</td>
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<td>Salamon et al, 2008¹⁵</td>
<td>Localization and outcomes</td>
<td>45</td>
<td>The 2004-2007 cohort in which FDG-PET/MRI coregistration studies were a routine part of presurgical evaluation were compared with pts from 2000-2003 without this technique Epilepsy pts with cortical dysplasia</td>
<td>Retrospective One cohort underwent combined modalities (PET/MRI), which was not available for the other</td>
<td>Not reported in the article</td>
<td>A cohort from 2000-2003 without the use of FDG-PET/MRI coregistration</td>
<td>Not reported</td>
<td>Combined PET/MRI detected more cortical dysplasia pts and fewer cases required intracranial EEG. More pts (2004-2007) had surgery compared to pts (2000-2003) 82% of pts (2004-2007) were seizure-free after surgery. PET/MRI coregistration enhanced the identification and successful surgical treatment of pts with cortical dysplasia, especially those with nonconcordant results and those with normal MRI scans</td>
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<tr>
<td>Kurian et al, 2007¹⁶</td>
<td>Localization and outcomes</td>
<td>50</td>
<td>Pediatric pts having drug-resistant epilepsy who underwent preoperative evaluation, surgery, and had post-operative follow-up at least</td>
<td>Retrospective All pts underwent EEG, MRI, PET and SPECT Surgical decision was based on</td>
<td>21M, 29F Mean age 10.2 ± 5.8 yrs Mean follow-up after surgery 21 months (range 12-48 months)</td>
<td>Single modality</td>
<td>Surgical outcome</td>
<td>Localization, concordant to the operation site: MRI (82%), PET (78%), SPECT (76%). Localization with more imaging modalities yielded</td>
<td>The combined use of multiple imaging modalities in the pre-surgical evaluation of pediatric epilepsy is</td>
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<td>Uijl et al, 2007</td>
<td>Localization</td>
<td>469</td>
<td>Consecutive pts referred to the national Dutch epilepsy surgery program between 1660 and 2002.</td>
<td>Retrospective Pts underwent FDG-PET, MRI or EEG</td>
<td>230M, 239F Mean age 32yrs</td>
<td>Single MRI or EEG</td>
<td>Not reported</td>
<td>higher benefit from surgical treatment compared to single modality. Concordance of focus localization by all three modalities was seen in 19/41 pts, and 95% of those pts had seizure-free outcome.</td>
<td>worthwhile and better for postoperative seizure control, especially when EEG and MRI alone are non-contributive.</td>
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<td>Ollenberger et al, 2005</td>
<td>Survey</td>
<td>118</td>
<td>Pediatric pts with refractory epilepsy having at least one</td>
<td>Retrospective</td>
<td>66M, 52F Mean age 7.3 yrs (range 0.5)</td>
<td>MRI, EEG and SPECT</td>
<td>Not reported</td>
<td>FDG-PET provided additional diagnosis value in decision-making for temporal lobe epilepsy surgery, especially when MRI or EEG monitoring are non-localizing.</td>
<td>FDG-PET has a definite role in the...</td>
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<td>FDG-PET scan between September 1992 and January 2000.</td>
<td></td>
<td>to 12.5 yrs</td>
<td>Surgical candidates (n=92) Medical management (n=21)</td>
<td></td>
<td></td>
<td>information to other investigations regarding epileptogenic sites in 77% of pts. PET scan results changed clinical management in 51% of pts, mainly those considered for surgery.</td>
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</tbody>
</table>

EEG: electroencephalogram; F: female; FDG: 18F-fluorodeoxyglucose; M: male; MRI: magnetic resonance imaging; NPV: negative predictive value; OR: odds ratio; PET: positron emission tomography; PPV: positive predictive value; Pts: patients; SAH: selective amygdalohippocampectomy; SISCOM: subtraction ictal SPECT coregistered to MRI; MSI: magnetic source imaging (magnetoencephalography-based source localization combined with MRI); SPECT: single photon emission computed tomography; yrs: years