

***Positron emission
tomography (PET)
for epilepsy***

November 2004

MSAC reference 26

Assessment report

© Commonwealth of Australia 2005

ISBN 0 642 82650 1

ISSN (Print) 1443-7120

ISSN (Online) 1443-7139

First printed May 2005

Paper-based publications

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Publication approval number: 3637 (JN8984)

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Glossary

Absence Seizure – A type of generalised seizure characterised by a stare, sometimes accompanied by blinking or brief movements of the mouth or hands. Previously known as petit mal.

Antiepileptic Drugs (AEDs) – Medications used for the control of seizures (also known as anticonvulsants).

Clonic Seizure – A type of seizure characterised by rhythmic jerks, usually generalised.

Complex Partial Seizure – A type of epileptic seizure that involves only part of the brain and results in impaired consciousness.

Electroencephalography (EEG) – A diagnostic test of electrical activity in the brain, used to help diagnose epilepsy.

Epilepsy – A broad spectrum of neurological conditions marked by recurrent (two or more), unprovoked seizures.

Epileptogenic – Causing epilepsy.

Focus – The site in the brain from which epileptic discharges originate.

Frontal Lobe – An area of the brain located in front of the central sulcus, and concerned with planning, emotions, parts of speech and movement, and problem solving.

Generalised Seizure – Seizures for which the clinical characteristics give no indication of anatomical localisation.

Hippocampus – A region of the brain occupying the internal aspect of the temporal lobe. It is believed to be the most seizure-prone region of the brain.

Hippocampal Sclerosis – A pattern of gliosis and loss of cortical neurons in the hippocampus. Also known as Mesial Temporal Sclerosis.

Ictal – Events occurring during an epileptic seizure.

Lateralisation – The localisation of an epileptogenic focus or foci to one hemisphere of the brain.

Localisation – The determination of a specific area or areas of the brain that produce an epileptogenic focus or foci.

Magnetic Resonance Imaging (MRI) – A diagnostic test using strong magnetic fields to create images of the body and brain. It is used in the diagnosis of epilepsy to detect lesions in the brain.

Mesial Temporal Sclerosis – see Hippocampal Sclerosis.

Myoclonic Seizure – Brief muscle jerk caused by abnormal electrical activity in the brain.

Occipital Lobe – An area of the brain located at the back of the brain, and concerned with aspects of vision.

Parietal Lobe – An area of the brain located in front of the central sulcus, and concerned with perception of touch, pressure, temperature and pain.

Positron Emission Tomography (PET) – A diagnostic test that uses various radiopharmaceuticals to create images of neurochemical processes and blood flow in the brain.

Refractory Epilepsy – Epilepsy that does not respond to Antiepileptic Drugs.

Single Photon Emission (Computed) Tomography (SPE(C)T) – A diagnostic test that uses various radiopharmaceuticals to create images of blood flow in the brain.

Status Epilepticus – An unvarying and enduring epileptic condition characterised by prolonged seizures or seizures at brief intervals.

Temporal Lobe – An area of the brain located below the lateral fissure, and concerned with hearing and memory.

Tonic Seizure – A type of seizure characterised by stiffening of the body. Consciousness is usually maintained.

Tonic-Clonic Seizure – A type of seizure characterised by loss of consciousness, falling, stiffening, and jerking. Previously known as grand mal.

Wada Test – A test that involves introducing sodium amobarbital to one hemisphere of the brain at a time, and recording the effects on cognitive functioning. The test can be useful for the lateralisation of epileptogenic foci, but is not currently practiced in Australia.

Executive summary

The procedure

Positron emission tomography (PET) is a minimally invasive method of nuclear medicine imaging that uses short-lived radiopharmaceuticals to detect and assess perfusion and metabolic activity in various organ systems. When compared to anatomical information that is provided by radiological techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and radiology, PET can provide information about function and metabolism that is complementary to the structural information provided by these techniques.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Australian Government Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the NHMRC Clinical Trials Centre was engaged to conduct a systematic review of literature on positron emission tomography (PET) imaging using the radionuclide 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG) for the indication of epilepsy. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of positron emission tomography for epilepsy

Clinical need

Australian statistics on the prevalence of epilepsy vary between 340 per 100,000 and 3,000 per 100,000 (Australian Institute for Health and Welfare 2000; Epilepsy Foundation of Victoria 2001). The Australian Institute of Health and Welfare (AIHW) estimated that epilepsy had an incidence of 30 per 100,000 and a mortality rate of 1 per 100,000 in 1996 (AIHW 2000).

In 2002-03, there were 18,006 hospital separations, translating to 58,150 patient days at an average length of stay of 4.1 days. Approximately 25% of epilepsy patients are refractory to medical treatment. A proportion of these will be considered for surgery. A minority of patients being considered for surgery will require further investigation after standard non-invasive testing (EEG and MRI).

Safety

PET is a noninvasive and safe diagnostic procedure. Safety issues are primarily discussed in terms of the safety of the positron-emitting radiopharmaceutical, rather than the safety of the procedure as a whole.

In a large study of 22 FDG PET centres in the United States, no adverse reactions to positron-emitting radiopharmaceuticals were reported retrospectively for 33,925 doses of positron-emitting radiopharmaceuticals from before 1994 and for 47,876 prospective doses from 1994 to 1997.

The United States Pharmacopoeia drug information for FDG also indicates that there are no known adverse effects associated with the use of FDG. In addition, radiotracers are generally used in microgram quantities, and as such the incidence of adverse reactions to very small amounts of labelled molecules is likely to continue to be low.

Patients undergoing a PET scan will be exposed to a certain amount of ionising radiation. It has been estimated that the radiation dose in a patient undergoing a FDG-PET scan is on par with that received during a diagnostic CT scan.

Effectiveness

There is no evidence from controlled trials about the effectiveness of PET in patients for whom EEG and MRI results are insufficient to proceed to surgery. Evidence from case series suggests that PET provides localisation information in some patients (median 70%, range 39-100%), and that some patients (median 67%, range 29-100%) have good post-surgical outcomes after having a PET scan in their presurgical workup (Level IV evidence). The accuracy of PET in this patient group cannot be estimated due to problems in defining a reference standard. A single study (Level IV) investigating the impact of PET on clinical management suggests that PET is promising in this regard. Any conclusions made by linking the evidence of extra localisation data provided by PET to improved surgical outcomes assume firstly that the efficacy of surgery is equivalent in patients with structural and functional foci, and secondly that PET results in altered management. If, based on current clinical expertise, these assumptions are judged to be reasonable, then it may be concluded that PET provides extra localisation information in some patients with medically refractory epilepsy, in whom MRI and EEG had not been able to localise a seizure focus, and that some of these patients will have good post-surgical seizure control outcomes. There is insufficient evidence to determine the size of this effect.

Cost effectiveness

A simple cost analysis suggests that the use of PET in the population of interest is likely to produce a cost saving in the long term. The analysis does not take into account the potential health benefits provided by the technology. Further evidence regarding the clinical effectiveness of PET is required before a formal cost-effectiveness analysis can be conducted.

Recommendation

In relation to positron emission tomography prior to surgery in patients with refractory epilepsy, where there is no focus with concordant results on usual structural imaging and electroencephalogram, this assessment finds the technology:

- is safe;
- provides additional localising information in some patients, for whom a proportion will have good post-surgical outcomes as a consequence; and
- is likely to be cost-effective in the long term.

MSAC recommends that public funding should be supported.

- The Minister for Health and Ageing accepted this recommendation on 2 March 2005.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of positron emission tomography (PET) imaging using the radionuclide 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG) as a diagnostic technology for the indication of *epilepsy*.

MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report updates the previous assessment of evidence for FDG-PET imaging in epilepsy (Reference 10) (MSAC 2000). The previous assessment recommended interim funding for PET for the evaluation of patients with refractory epilepsy who are being considered for surgery in a comprehensive epilepsy program, where there is inconclusive localising information from standard assessment, including seizure semiology, electroencephalography and magnetic resonance imaging.

Background

Positron Emission Tomography

How it works

PET is a minimally invasive method of nuclear medicine imaging that uses short-lived radiopharmaceuticals to detect and assess perfusion and metabolic activity in various organ systems. It provides information about function and metabolism that is complementary to the structural information provided by traditional imaging techniques such as radiology (Prvulovich & Bomanji 1998).

The majority of radioactive isotopes used in nuclear medical imaging release energy as single gamma rays (photons) as they decay. Conventional nuclear medical imaging is based upon the detection of these photons using stationary single or multi-headed gamma cameras that produce two-dimensional images. Tomographic techniques such as single photon emission (computed) tomography (SPE(C)T) can use rotating camera heads to acquire imaging data in a 360° circle around the patient, from which multiple cross-sectional images are reconstructed (Flynn & Adams 1996).

PET is a related technology that uses radioisotopes which decay by emitting a positively charged electron (positron) from the nucleus. The positron annihilates a negatively charged electron, resulting in two high-energy photons (511 kilo-electron-volts, keV) that travel at 180 degrees to each other. The high-energy photon is subject to less absorption or scatter by tissue than the comparatively lower-energy photons released during conventional nuclear medicine imaging, and is detected in coincidence with its pair, which usually results in superior image quality (Lewellen, Miyaoka, & Swan 1999).

A positron camera is typically arranged in a ring around the patient and produces cross-sectional tomographic images. Traditional PET scanners come in full-ring and more recently partial-ring models (Adams et al 1999). Robert and Milne (1999) described four ways of describing PET scanners:

- traditional full-ring PET systems;
- partial-ring rotating PET scanners;
- coincidence imaging with modified gamma camera technology;
- high-energy collimator imaging of 511 keV photons with modified gamma camera technology.

Studies reported in the main body of this submission have used traditional full-ring PET scanners. Results from these systems can be further subclassified according to whether or not they acquire data in two or three dimensions and the mode (if any) of attenuation correction.

Earlier scanners have a relatively low resolution and would be expected to yield a high positive predictive value and a lower negative predictive value. Overall accuracy with

such scanners would be expected to be lower than more recent scanners. All modern scanners use attenuation correction obtained through maps generated by the attenuation of gamma rays from either single photon or positron-emitting radionuclides, or X-rays in PET/CT scanners.

Charged particle accelerators (eg generators and cyclotrons) produce the radiopharmaceuticals used for PET scanning. The particles principally used include oxygen (^{15}O), nitrogen (^{13}N), carbon (^{11}C) or fluorine (^{18}F). This review is restricted to an examination of the radionuclide ^{18}F -FDG (2- ^{18}F fluoro-2-deoxy-D-glucose), which is a radiolabelled analogue of glucose. This radionuclide is useful for imaging in neurology, and epilepsy specifically, because an epileptogenic seizure focus tends to display decreased glucose utilisation interictally, and ^{18}F -FDG can be used to examine the decreased metabolism of potentially epileptogenic areas compared with nonepileptogenic areas (Immonen et al 2004).

Dual-modality PET/CT scans have recently been introduced. Such systems allow for PET emission data to be routinely corrected for photon attenuation by CT, thus producing noiseless attenuation correction and reduced scanning times when compared with PET (Carney & Townsend 2003). The reduction in scanning time is reported to be in the order of 25-30% (Schulthess 2003). An additional benefit is the production of detailed anatomical information by CT which is absent on PET scans. These “hardware” coregistered images can aid in diagnostic interpretation. The coregistration of PET and CT images in a single system is reported to be more time-efficient and provide a higher level of image quality than software coregistration of images (Schulthess 2003).

A full discussion of the extent to which PET technology is used in Australia is available in the *Report of the review of positron emission tomography* (Commonwealth Department of Health and Aged Care 2001).

The Procedure

Patients are asked to fast for five to six hours on the day of their scan. Upon arrival, FDG is injected via an intravenous cannula placed in the patient’s arm. After the injection of FDG the patient waits up to an hour before undergoing the scan. This allows the FDG tracer to accumulate in normal brain areas. Abnormal brain areas (corresponding to epileptogenic seizure foci) have reduced FDG accumulation (hypometabolism). The patient is then scanned. The scan takes between fifteen and thirty minutes to complete (Dussault et al 2001).

Intended purpose

PET is intended to image the functional/metabolic activity of neurological structures and aid in the diagnosis and treatment planning for medically refractory epilepsy.

Incremental or replacement test?

In clinical practice, PET is often used in patients with medically refractory epilepsy as an incremental test in addition to conventional imaging (eg MRI etc.), rather than as a replacement test for one of these imaging modalities. Further, PET results are often evaluated after conventional imaging, and with those results available, ie PET

information is generally not interpreted independently of results of conventional imaging when it is used in clinical decision making. In patients with medically refractory epilepsy the Advisory Panel advised that the role of PET would be as an incremental test in patients where prior tests were discordant or insufficient to plan surgery.

Potential impact

In this intended role, the potential benefits of PET have been identified as:

- to localise the seizure focus;
- to change patient management from not eligible for surgery to eligible for surgery (or to optimise the planned surgical approach);
- to improve long term patient health outcomes as a result of surgical management
- to reduce the long term costs of medical care and ongoing medication as a result of surgical management; and
- to reduce the use of other costly or potentially harmful tests eg invasive EEG testing.

The potential harms or costs of PET for this purpose are:

- the consequences of inappropriate surgery due to false positive findings; and
- the additional cost of PET for this patient group.

Consideration of the trade-offs between these costs and benefits suggest that any cost offsets resulting from PET relate primarily to the avoidance of ongoing treatments for patients with medically refractory epilepsy who can be successfully managed with surgery on the basis of the additional information provided by PET.

Issues in evaluation of PET

Evaluation of diagnostic tests

Several authors have discussed the sequence of evaluations that can be carried out for a diagnostic test (Jaeschke, Guyatt, & Sackett 1994; Guyatt 1986; Fryback 1991). These include diagnostic test performance, therapeutic impact and outcome.

Diagnostic test performance ('accuracy') can be measured as sensitivity, specificity, or likelihood ratios. This involves comparing test results against a valid reference or 'reference standard' which represents the 'truth'. Appropriate reference standards can include pathology findings (for example, histopathological confirmation of the presence or absence of disease) or clinical outcome (for example, subsequent disease progression or resolution of symptoms and signs).

Therapeutic impact is measured as the change in treatment decisions made by clinicians in response to the information provided by the test. This may be a decision to start, stop, modify or continue therapy.

Outcome can be assessed by randomised trials of the test and subsequent management resulting from test information. As these studies are often not available, changes in

health outcomes may be reasonably inferred from a combination of evidence of improved diagnostic accuracy, evidence of changes in management and evidence of the effective treatment of a given condition. That is, in conjunction with evidence of improved diagnostic accuracy and changes in management, there should be evidence (ideally from randomised controlled trials) that alternative treatments or managements result in improved long term health outcomes for patients. For example, if a diagnostic test allowed earlier diagnosis of a condition, evidence that earlier treatment is more effective than delayed treatment would be needed to infer that the diagnostic test results in improved health outcomes.

Methodological constraints may prevent some of these studies being undertaken. For example, if it is not possible to measure a valid reference standard, studies of diagnostic test performance characteristics are compromised.

Flow diagrams showing the suggested pathway by which testing should improve outcomes is a helpful way of summarising why we expect a test may be valuable. Studies done for each step or for groups of steps can be appraised and the quality of the evidence noted. Flow diagrams can also assist in clarifying the specific clinical question which is being considered.

Clinical need/burden of disease

Definition and classification

Epilepsy is not a single disease, but rather is a broad spectrum of neurological conditions marked by recurrent (two or more), unprovoked seizures (Holmes & Miller 2004). Two seizures within a 24 hour period are considered a single event, as is an episode of status epilepticus (Hopkins & Shorvon 1995). Seizures themselves are defined as clinical manifestations assumed to result from abnormal and excessive discharges of a set of neurons in the brain. Such clinical manifestations are sudden and transitory abnormal phenomena including alterations of consciousness, motor, sensory, autonomic or psychic events that are perceived either by the patient or an observer.

Broadly speaking, epilepsy may be classified based on whether seizures are associated with brain lesions or other abnormalities. When associated with such lesions or abnormalities, epilepsy is said to be symptomatic; when no lesion is evident the condition is known as idiopathic epilepsy (D'Ambrosio 2004).

The International League Against Epilepsy (ILAE) has developed a classification system for epileptic seizures based on clinical and electroencephalographic characteristics (Commission on Classification and Terminology of the International League Against Epilepsy 1981) (Table 1). Epileptic seizures can be categorised as either partial (where the seizure is generated from focal brain regions with variable spread to adjacent or distant areas of the brain) or generalised (where seizures appear to begin in both hemispheres of the brain). These categorisations may be further subdivided based on symptoms such as the impairment of consciousness. For example, simple partial seizures involve no impairment of consciousness, but may involve motor, somatosensory, autonomic or psychic symptoms (D'Ambrosio 2004). Complex partial seizures involve impairment of consciousness. They may begin as simple partial seizures and then progress to complex seizures. Generalised seizures can be further sub-classified as absence (sudden onset and

end), myoclonic (sudden shock-like muscle contractions), tonic (sustained muscle contractions), clonic (repetitive muscle contractions), atonic, or tonic-clonic.

Furthermore, ILAE has developed a classification of epilepsies and epileptic syndromes based on cause (idiopathic, symptomatic, cryptogenic) and anatomy (localisation-related or generalised) (Commission on Classification and Terminology of the International League Against Epilepsy 1989) (Table 2). The classification also recognises that some syndromes cannot currently be classified as either localisation-related or generalised, and acknowledges situation-related syndromes. ILAE has drafted proposed revisions to its original classifications of seizures and epilepsy (Engel & International League Against Epilepsy 2001), but these do not yet appear to have been generally accepted.

Table 1 ILAE classification of epileptic syndromes

<p>I. Partial seizures</p> <ul style="list-style-type: none">A. Simple partialB. Complex partial<ul style="list-style-type: none">1. Impairment of consciousness at onset2. Simple partial onset progressing to complex partialC. Partial seizures evolving to generalised tonic-clonic convulsions<ul style="list-style-type: none">1. Simple partial evolving to generalised tonic-clonic convulsions2. Complex evolving to generalised tonic-clonic convulsions, including those with partial onset <p>II. Generalised seizures</p> <ul style="list-style-type: none">A. AbsenceB. MyoclonicC. TonicD. ClonicE. AtonicF. Tonic-clonic <p>III. Unclassified</p>

Table 2 ILAE classification of epilepsy and epileptic seizures

<p>I. Localisation-related</p> <p>A. Idiopathic (with age-related onset)</p> <ol style="list-style-type: none">1. Benign childhood epilepsy with centrotemporal spikes2. Childhood epilepsy with occipital paroxysms3. Primary reading epilepsy <p>B. Symptomatic</p> <ol style="list-style-type: none">2. Chronic progressive epilepsia partialis continua of childhood <p>C. Cryptogenic</p> <ol style="list-style-type: none">1. Temporal lobe epilepsies2. Frontal lobe epilepsies3. Parietal lobe epilepsies4. Occipital lobe epilepsies5. Bilobar and multilobar epilepsies <p>II. Generalised</p> <p>A. Idiopathic (with age-related onset)</p> <ol style="list-style-type: none">1. Benign neonatal familial convulsions2. Benign neonatal convulsions3. Benign myoclonic epilepsy in infancy4. Childhood absence epilepsy5. Juvenile absence epilepsy6. Juvenile myoclonic epilepsy7. Other idiopathic generalised epilepsy syndromes not defined8. Epilepsies with seizures precipitated by specific modes of interaction <p>B. Cryptogenic or symptomatic (in order of age)</p> <ol style="list-style-type: none">1. West syndrome2. Lennox-Gastaut syndrome3. Epilepsy with myoclonic-astatic seizures4. Epilepsy with myoclonic absence <p>C. Symptomatic</p> <ol style="list-style-type: none">1. Early myoclonic encephalopathy2. Early infantile epileptic encephalopathy with burst-suppression3. Other symptomatic generalised epilepsies not defined above4. Specific syndromes <p>III. Epilepsies and syndromes undetermined as to whether focal or generalised</p> <p>IV. Special syndromes</p> <p>A. Situation-related</p> <ol style="list-style-type: none">1. Febrile seizures2. Isolated seizures or isolated status epilepticus3. Acute symptomatic seizures (eg secondary to metabolic or toxic factors)
--

Burden of disease

The World Health Organisation (WHO) estimates that globally there are approximately 50 million people who suffer from epilepsy (WHO 2001). It has been estimated that epilepsy resulted in 125,000 deaths in 2002 (0.2% of total deaths), and that the global

burden of disease for epilepsy was 7,328,000 disability-adjusted life years (DALYs) (0.5% of total DALYs) (WHO 2004).

Australian statistics on the prevalence of epilepsy vary. The Australian Institute of Health and Welfare (AIHW) estimated that epilepsy (defined as recurrent – two or more – unprovoked seizures) had a prevalence of 340 per 100,000 in 1996 (AIHW 2000), whereas the Epilepsy Foundation of Victoria estimated the prevalence to be 3,000 per 100,000 (Epilepsy Foundation of Victoria 2001). According to the National Health Survey conducted in 2001, 120,300 people self-reported as having epilepsy in Australia (Australian Bureau of Statistics 2002).

AIHW data suggest that in Australia epilepsy has an incidence of 30 per 100,000 and a mortality rate of 1 per 100,000 (AIHW 2000).

Although responsible for relatively few deaths, there were 17,512 epilepsy-related hospitalisations in 2001-02. Table 3 presents epilepsy-related hospital separations in 2001-02, broken down by age and specific ICD-10-AM code (AIHW 2004). In 2002-03, there were 18,006 separations, translating to 58,150 patient days at an average length of stay of 4.1 days. Table 4 reports epilepsy-related hospital separations in 2002-03, along with patient days and average length of stay, broken down by hospital type (public vs. private) (AIHW 2004). The estimated health system costs for epilepsy in 1993-4 were over \$157 million (AIHW 2000).

Although data for medically refractory epilepsy are unavailable, it is estimated that this group comprises approximately 25% of the total population of patients with epilepsy. Hence, it is likely that patients with medically refractory epilepsy are responsible for at least 25% of the resource use figures presented above, with some estimates suggesting this may be as high as 40% (Pilcher 2004). A proportion of medically refractory epilepsy patients will be considered for surgery. A minority of patients being considered for surgery will require further investigation after standard non-invasive testing (EEG and MRI). Current utilisation data for PET indicates that the impact of the test on total burden of disease is likely to be modest. There were 155 and 248 scans reimbursed through the MBS in 2002 and 2003, respectively.

Australian Hospital Statistics data for 2002-03 report that there were 16 specialised refractory epilepsy units in Australia (6 in Victoria, 5 in New South Wales, 3 in Western Australia, and 2 in South Australia). All units were located in major cities (AIHW 2004).

Table 3 Epilepsy-related hospitalisations in 2001-02 by age and ICD-10-AM code

Disease (ICD-10-AM code)	Age group					
	<15	15-34	35-54	55-74	75+	All ages
G40.0 Localization-related (focal)(partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset	24	1	7	0	2	34
G40.1 Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures	230	136	145	144	102	757
G40.2 Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures	278	321	271	115	92	1077
G40.3 Generalized idiopathic epilepsy and epileptic syndromes	835	1025	903	450	253	3466
G40.4 Other generalized epilepsy and epileptic syndromes	238	76	34	8	2	358
G40.5 Special epileptic syndromes	7	77	115	35	4	238
G40.6 Grand mal seizures, unspecified (with or without petit mal)	268	862	825	376	186	2517
G40.7 Petit mal, unspecified, without grand mal seizures	22	23	35	15	15	110
G40.8 Other epilepsy	124	67	68	30	15	304
G40.9 Epilepsy, unspecified	1384	2063	2093	1052	583	7176
G41.0 Grand mal status epilepticus	127	141	150	53	38	509
G41.1 Petit mal status epilepticus	9	7	4	5	4	29
G41.2 Complex partial status epilepticus	16	28	34	9	4	91
G41.8 Other status epilepticus	37	13	17	18	12	97
G41.9 Status epilepticus, unspecified	275	130	186	106	52	749
All epilepsies (G40-41)	3874	4970	4887	2416	1364	17512 ^a

^a Total includes one male patient with Epilepsy, unspecified (G40.9) with age not recorded.

Table 4 Epilepsy-related hospitalisations in 2002-03 by hospital type (public vs. private)

Principal diagnosis	Separations	Same day separations	Public patient separations	Separations per 10,000 population	Patient days	Patient days per 10,000 population	ALOS (days)	ALOS (days) excluding same day
Public hospitals								
G40 Epilepsy	15,437	4,534	13,993	7.8	44,280	22.4	2.9	3.6
G41 Status epilepticus	1,362	216	1,229	0.7	7,548	3.8	5.5	6.4
Total	16,799	4,750	15,222	8.5	51,828	26.2	3.1	3.9
Private hospitals								
G40 Epilepsy	1,126	104	180	0.6	5,831	3.0	5.2	5.6
G41 Status epilepticus	81	6	18	<0.1	491	0.2	6.1	6.5
Total	1,207	110	198	0.6	6,322	3.2	5.2	5.7
TOTAL	18,006	4,860	15,420	9.1	58,150	29.4	3.2	4.1

Medical management

The treatment of epilepsy with antiepileptic drugs (AED) is typically initiated when the risks to the patient of recurrent seizures are assessed to exceed those associated with treatment (Yamatogi 2004). In general, medical management follows the following principles:

- Confirmation of diagnosis of epilepsy;
- Accurate classification of epileptic seizures and epileptic syndromes;
- Selection of AED according to classification;
- Initiation of AED, with initial monotherapy of small dose with gradual increase being preferable;
- Adjustment to lowest effective dose of fewest possible AEDs, with monitoring of seizures, epileptic discharges and adverse events;
- Long-term regular AED intake; and
- Trial discontinuation of AED for those with prolonged suppression of seizures and epileptic discharges.

The choice of AED treatments depend largely on seizure classification (Shorvon 1995). Drugs of choice for partial epilepsy with listing on the Pharmaceutical Benefits Scheme (PBS) include carbamazepine, phenytoin, and primidone. Ethosuximide, valproate, and benzodiazepines such as clonazepam are utilised in the treatment of generalised epilepsies, while benzodiazepines and valproate are used for both partial and generalised epilepsies (Yamatogi 2004). The AEDs with PBS approval at the time of publication, along with their approved indications, are listed in Table 5 (Department of Health and Ageing 2004).

Table 5 Anti-epileptic medications listed on the Pharmaceutical Benefits Scheme (PBS)

Drug Name	Proprietary Name	Restricted Benefit	Authority Required
Phenobarbitone		Epilepsy	
Phenobarbitone Sodium		Epilepsy	
Primidone	Mysoline		
Phenytoin	Dilantin; Dilantin Infatabs		
Phenytoin Sodium	Dilantin Sodium		
Ethosuximide	Zarontin		
Clonazepam (injection preparation)	Rivotril	Epilepsy	
Clonazepam (tablet and oral liquid preparations)	Paxam 0.5; Paxam 2; Rivotril		Neurologically proven epilepsy
Nitrazepam	Alodorm; Mogadon		Myoclonic epilepsy
Carbamazepine	Carbamazepine BC; Carbamazepine Sandoz; Tegretol 100; Tegretol 200; Tegretol CR 200; Tegretol CR 400; Tegretol liquid; Teril		
Oxcarbazepine	Trileptal		Treatment of partial epileptic seizures and primary generalised clonic-tonic seizures, which are not controlled satisfactorily by other anti-epileptic drugs
Sodium Valproate	Epilim; Epilim EC; Epilim Liquid; Epilim Syrup; Valpro 200; Valpro 500		
Tiagabine Hydrochloride	Gabitril		Treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs
Vigabatrin	Sabril		Treatment of epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs
Gabapentin	Gantin; Neurontin; Neurontin 100; DBL Gabapentin; Douglas Gabapentin 300mg; Douglas Gabapentin 400mg; GenRx Gabapentin; Nupentin 300; Nupentin 400; Pendine 300; Pendine 400; Pendine 800		Treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs
Lamotrigine	Lamictal		Treatment of epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs
Levetiracetam	Keppra		Treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs
Sulthiame	Ospolot		
Topiramate	Topamax; Topamax Sprinke		Treatment of partial epileptic seizures, primary generalised tonic-clonic epileptic seizures and seizures of the Lennox-Gastaut syndrome, which are not controlled satisfactorily by other anti-epileptic drugs

AED therapy often requires that the patient take medication continuously for many years, often in combination. Side-effects may occur, and these can be divided into acute (dose-related) effects, hypersensitivity reaction and chronic toxic effects (Shorvon 1995). Acute and hypersensitivity reactions are often easily recognised, however chronic toxic effects may be variable and unpredictable, and hence difficult to detect.

It has been estimated that at least 25% of epilepsy patients do not respond to medical treatment (Holmes & Miller 2004). Such patients are said to be medically refractory or intractable, defined as the continuation of recurrent seizures despite optimum treatment supervised by an experience neurologist over a period of 2-3 years (Cosgrove & Cole 2004). It is rare for medically refractory epilepsy patients to spontaneously improve without further intervention. Patients who are refractory to medical treatment may be considered candidates for surgical management.

Surgical management

The objective of surgical treatment of epilepsy is the complete resection of the epileptogenic zone, the area responsible for the occurrence of clinical seizures (Hadar & Luders 2004).

Pre-surgical evaluation for epilepsy surgery is a complex process, requiring the integration of information from numerous sources including the clinical history, which may provide valuable seizure localisation information (Cosgrove & Cole 2004). The evaluation algorithm is partially determined by the clinician's "levels of confidence" in the diagnosis, factoring in such variables as the severity of epilepsy and the extent to which exact localisation of a lesion or lesions is possible.

A general taxonomy of surgically remediable epilepsy syndromes (see Table 6) suggests that the syndrome most amenable to surgery is temporal lobe epilepsy, either idiopathic, with mesial temporal sclerosis/mesial temporal lobe epilepsy, or lesional (tumour, vascular malformation, developmental, ischaemic, or traumatic). Table 7 outlines the various surgical approaches currently available. Resective surgery is generally the surgical option most appropriate for focal medically refractory temporal and extratemporal lobe epilepsies.

Table 6 Surgically remediable medically refractory epilepsy syndromes

Temporal Lobe Epilepsy	Idiopathic Mesial temporal sclerosis/mesial temporal lobe epilepsy Lesional (tumour, vascular malformation, developmental, ischaemic, traumatic)
Extratemporal Epilepsy	Idiopathic Lesional (tumour, vascular malformation, developmental, ischaemic, traumatic)
Catastrophic Epilepsy	Lesional (hemimegalencephaly, diffuse cortical dysplasias, Surge-Weber, Rasmussen's, porencephalic cysts)
Secondary Generalised Epilepsies	Lennox-Gastaut

Source: Pilcher (2004)

Table 7 Surgical approaches for medically intractable epilepsy

Resective Surgery	Temporal lobe resections (“standard”, anteromedial selective amygdalohippocampectomy) Extratemporal resections – lesional resections, anatomic or functional hemispherectomy
Radiosurgery	Mesial temporal lobe epilepsy Hypothalamic hamartomas with gelastic seizures
Disconnection Surgery	Corpus callosotomy Keyhole hemispherotomies Multiple subpial transections
Neuroaugmentative Surgery	Vagal Nerve Stimulator (VNS) Deep Brain Stimulation (DBS)
Diagnostic Surgery	Depth electrodes Subdural strip electrodes Subdural grid electrodes

Source: Pilcher (2004)

Post-surgical outcomes of seizure reduction are typically evaluated in terms of the Engel classification scheme, which outlines four categories of post-operative seizure outcome (Table 8) (Engel et al 1993). Class I denotes that the patient is free of disabling seizures for a period of two years or greater. Class II denotes a patient with rare disabling seizures (two or three per year). Class III indicates that a patient has had worthwhile improvement in seizure control (>90% reduction), while Class IV patients have had no worthwhile improvement (<90% reduction).

Research has demonstrated the efficacy of surgical treatment of intractable epilepsy, although quantification of the benefit in terms of seizure reduction has varied widely. In a comprehensive literature review of studies published between 1991 and 2000 (Medline search supplemented by hand searching), the median percentage of seizure-free patients after temporal lobectomy was found to be 70%, with a range of 33-93% (McIntosh, Wilson, & Berkovic 2001). Follow-up in these studies ranged from 0.2 to 30 years, and the “middle of the range” was 2.9 years. More recent studies tended to report better outcomes. Factors such as preoperative hippocampal sclerosis on MRI, anterior temporal localisation of interictal epileptiform activity, absence of preoperative generalised seizures, and absence of seizures in the first post-operative week appeared to be associated with good outcomes. Furthermore, in a controlled trial of 80 temporal lobe epilepsy patients randomised to surgery versus medical treatment, it was found that 58% of the surgical group were seizure-free after one year, compared with 8% of the medically managed group (Wiebe et al 2001).

More recent investigations of seizure control after surgery demonstrate the variation in reported outcomes. At the upper end of the spectrum, Lowe et al (2004) examined a cohort of 50 patients with pathologically proven hippocampal sclerosis who had temporal lobectomies for treatment of temporal lobe epilepsy, and were followed up for two years or longer. Freedom from seizures (Engel’s class I) was achieved in 83% of patients. Stavem et al (2004) reported that 44% of 63 patients undergoing anterior temporal lobectomy for intractable epilepsy had class I outcomes after two-year post-surgical follow-up. In a larger sample (N = 355) where the post-surgical follow-up was only one year, Spencer et al (2003) reported that 77% of patients with medial temporal resections and 56% of patients with neocortical (including temporal neocortex) resections achieved freedom from seizures.

It should be noted that since temporal lobe epilepsies are more amenable to surgical resection, the percentage of positive surgical outcomes following extratemporal resective

surgery is likely to be lower than those reported above (Pilcher 2004). In an international survey of data from 100 epilepsy surgery centres collected between 1986 and 1990, Engel (1996) found the percentage of patients who were seizure-free after temporal lobe resection (approximately 68%) to be greater than that after extratemporal resection (approximately 45%). However, it is possible that some improvement in seizure control after extratemporal resection may have occurred since this survey was conducted.

Epilepsy surgery is generally considered to be safe, and complications associated with surgery are relatively rare. Uncommon complications have been reported and include death, infection, hemiparesis, visual field defects, hematoma formation, and cranial nerve III and cranial nerve IV palsies (Pilcher 2004). Less than 5% of patients experience post-operative neurologic deficit, with the majority of these being transient and resolving within a period of months (Engel 1996).

There is evidence to suggest a trend to decreased surgical mortality and morbidity in more recent studies. In a series of 321 patients who underwent surgery for temporal lobe epilepsy, Clusman et al (2002) reported 28 surgical complications (8.5%), none of which had permanent sequelae. Neurological complications occurred in 17 patients (5.2%), with eight of these (2.4%) resulting in transient morbidity. There were no intraoperative deaths. Weibe et al (2001) reported no deaths at twelve months follow-up in the surgically treated arm of their randomised controlled trial, compared with one sudden unexplained death in the medically treated arm.

Table 8 Engel et al's (1993) classification of postoperative seizure outcome

Class I: Free of disabling seizures^a
A Completely seizure-free since surgery
B Nondisabling simple partial seizures only since surgery
C Some disabling seizures since surgery, but free of disabling seizures for at least 2 years
D Generalised convulsion with antiepileptic drug withdrawal only
Class II: Rare disabling seizures ("almost seizure-free")
A Initially free of disabling seizures but has rare seizures now
B Rare disabling seizures since surgery
C More than rare disabling seizures after surgery, but rare seizures for at least 2 years
D Nocturnal seizures only
Class III: Worthwhile improvement^b
A Worthwhile seizure reduction
B Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years
Class IV: No worthwhile improvement
A Significant seizure reduction
B No appreciable change
C Seizures worse

^a Excludes early postoperative seizures (first few weeks).

^b Determination of "worthwhile improvement" will require quantitative analyses of additional data such as per cent seizure reduction, cognitive function, and quality of life.

Existing investigative procedures

Electroencephalography (EEG)

Electroencephalographic (EEG) recording refers to a method of detecting, amplifying, filtering, displaying, storing and analysing small changes in electrical potential produced by neurological structures (Fish 1995). EEG recordings may be obtained in several ways. Routine EEG is a non-invasive method of monitoring electrical activity in the brain, and

involves placing electrodes on the scalp in standard positions. It is typically performed while the patient is awake and resting, over a period of 20-30 minutes in the interictal state (ie between seizure events). Video EEG involves the placement of electrodes on the scalp to monitor activity during (ictal) or between seizure events, with simultaneous video recording of the patient. Video EEG typically takes place over an extended time period (between 24 hours and 14 days) since although some interictal activity may be instructive for localisation purposes, it is generally accepted that it is important to record the ictal EEG over several seizure events.

When video EEG and other neuroimaging tests fail to conclusively localise a seizure focus, an invasive (intracranial) EEG may be indicated. Intracranial electrode placement provides more precise EEG information due to greater proximity to discharge regions and the reduction of artefacts involved with motion and muscles (Cosgrove & Cole 2004). Invasive EEG may involve epidural, subdural or intracerebral (depth) electrode placement.

Epidural electrode placement is associated with a small risk of infection; however the spatial resolution is limited, and is generally only used for lateralisation and approximate localisation. Subdural electrodes can record from a relatively wide area of the cortical surface, but cannot record directly from the deep cerebral structures, and carry with them a risk of infection (approximately 4%). Intracerebral electrode placement is conducted with guidance by MRI, CT or angiography. It is typically indicated for patients with bitemporal, bifrontal, or frontal temporal seizures, and can localise seizure onset zones to an extent not possible through scalp EEG. However, there is the risk of major complications (haemorrhage and infection) with associated morbidity and mortality (between 1% and 4%). Such risks are greater than those of resective surgery itself, and thus intracerebral EEG is conducted only when necessary.

There may be considerable inter-individual variation in EEG results, however in general, interictal epileptiform abnormalities take the form of spikes (20-70 ms in duration) or slow waves (70-200 ms in duration), whereas ictal abnormalities are characterised by a sustained discharge that is rhythmic and clearly different from interictal patterns (Fish 1995).

Neuropsychological testing

Neuropsychological testing of patients suffering from epilepsy aims to help in localisation of specific focal or multi-focal cognitive defects. These, when considered together with neuroimaging and EEG findings, provide a baseline for comparison with post-surgical evaluation (Cosgrove & Cole 2004). Neuropsychological test batteries usually include tests that provide specific information about the functioning of the brain, and those that provide more general contextual information (Dodrill 2004). The former include tests of specific functions (eg lateralised motor functions, language, verbal or visual memory) and tests of general brain condition (problem solving, attention and concentration). Tests providing more contextual information may include those measuring general intelligence, academic knowledge, lateral preference, and emotional or psychological functioning (Dodrill 2004).

Wada test/intracarotid amobarbital procedure (IAP)

The Wada test was named after its founder in 1954, but the term intracarotid amobarbital procedure (IAP) is considered more technically accurate (Dodrill 2004). The procedure

involves the introduction of sodium amobarbital to the arterial system of one cerebral hemisphere, followed by testing to determine the impact on cognitive functioning. The test is generally used for the evaluation and lateralisation of speech and memory function, but may provide valuable information for lateralising epileptic focus, predicting postoperative seizure control, identifying the likely extent of hippocampal sclerosis, and distinguishing between lateral neocortical and mesial temporal lobe epilepsy. The Wada test is not currently performed in Australia due to the unavailability of amobarbital.

Computed tomography (CT)

Computed tomography (CT) was the first cross-sectional neuroimaging technique able to localise structural epileptogenic lesions. However, in recent times CT has been almost completely replaced by high resolution magnetic resonance imaging (MRI) for the pre-surgical evaluation of intractable epilepsy at major epilepsy centres (Bronen 2004). This is due to evidence suggesting greater accuracy of MRI in medically refractory patients, combined with decreased costs and risk of complications associated with reduced need for intracranial EEG after MRI compared with CT. However, it is likely that all patients in Australia will have undergone CT at some point prior to referral to an epileptologist.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) uses the physical properties of unpaired hydrogen protons in different chemical, structural and magnetic environments to produce images of neurological tissues. MRI subjects the patient to a strong external magnetic field, causing hydrogen protons to align, and then to a radiofrequency pulse which excites the protons to a higher energy state and causes them to spin in phase (resonance). When the pulse is removed, the protons release this energy as radio waves, inducing an electric current that is measured as a signal in the receiver coils of the MRI scanner (Macdonald & Peduto 2000; Yochum & Barry 1996). This is known as relaxation, and may be measured in two ways. T1-relaxation is measured as the time for protons to realign along the direction of the magnetic field after a radiofrequency pulse. T2-relaxation is the time for the transverse magnetisation to de-phase after a pulse. The timing and strength of the radiofrequency pulse can be varied to emphasise either T1-relaxation (T1-weighted) or T2-relaxation (T2-weighted) in order to optimise imaging.

Several MRI scanning protocols for epilepsy have been developed, however most protocols use a high resolution, three-dimensional, heavily T1-weighted acquisition of the whole brain (Kim, Prost, & Lindell 2004). Specific tailored protocols are required for the detection of structural abnormalities such as mesial temporal sclerosis and subtle cortical and subcortical migration anomalies, as these may not be detected by routine MRI due to both their small size and signal characteristics, ie they may otherwise appear similar to the adjacent normal brain tissue.

Functional MRI (fMRI) is also currently used to localise eloquent cortex. The role and function of MRI is increasing and it therefore may play a more significant role in the future.

Single-photon emission (computed) tomography (SPE(C)T)

Single-photon emission computed tomography (SPECT) is a cross-sectional imaging technique that is based on the distribution of single-photon emitting radiotracers, most commonly technetium 99m. Other radiotracers can be used including thallium 201,

indium 111, iodine 131, iodine 123, and gallium 67 (Turkington & Gilland 2003). Radiation from these single-photon emitters is measured using a gamma camera.

SPECT provides a non-invasive measure of regional cerebral blood flow. Patients with focal seizure activity typically have reduced blood flow to the relevant temporal lobe, and frequently the whole hemisphere. SPECT can be used to assess cerebral blood flow during a seizure. Hyperperfusion is typically seen during seizure activity, particularly in the medial part of the temporal lobe. Hyperperfusion persists post-ictally in mesial temporal structures, combined with hypoperfusion in the lateral temporal cortex. Ictal SPECT is, however, logistically difficult to perform due to the requirement for trained staff to constantly monitor the patient and to administer radiotracer injection during the seizure.

SPECT has the advantage of employing longer life radiotracers than PET (six hours compared with two hours), and hence does not require an on-site cyclotron.

Current reimbursement arrangement

Medicare rebates are currently available for specific PET indications performed at seven designated full-ring PET facilities nationally. The designated centres are the Royal Prince Alfred and Liverpool hospitals in New South Wales, the Peter MacCallum Cancer Institute and Monash Medical Centre in Victoria, the Royal Adelaide Hospital in South Australia, the Wesley Hospital in Queensland and the Sir Charles Gairdner Hospital in Western Australia.

In addition, the Australian Government funds PET scans at the Austin Hospital, Melbourne, through a grant arrangement.

Approach to assessment

Formulation of the review question

The population of interest, index test, reference standard, comparator and outcomes were used to structure the research question.

Population

The population of interest was patients with epilepsy refractory to medical treatment being considered for surgery, for whom MRI was unable to localise a seizure focus (ie MRI “negative”), or for whom MRI and EEG results were nonconcordant. MRI is considered “negative” when results are normal.

Index test

The index test assessed by this review is full-ring PET using the radiotracer FDG.

The reference standard

This review includes studies validating FDG-PET against surgical outcome for patients undergoing surgery. No reference standard is available for patients not undergoing surgery.

Comparator

This report compares standard pre-surgical evaluation (consisting of at minimum MRI and scalp EEG) with the addition of FDG-PET to standard pre-surgical evaluation without FDG-PET.

Outcomes

The outcomes assessed by this review are:

- Safety;
- Diagnostic yield (localisation);
- Accuracy (“correct” localisation, and PET-positive patients with good outcomes);
- Changes in clinical management;
- Health outcomes (seizure control); and
- Costs.

The review question

The clinical question addressed by this review is:

- What is the value of PET prior to surgery in patients with refractory epilepsy where there is no focus with concordant results on usual structural imaging and EEG?

Review of literature

The medical literature was searched to identify relevant studies and reviews for the period between 1999 and June 2004, in order to update the previous MSAC assessment (Medicare Services Advisory Committee 2000). Searches were conducted via the following databases:

- Medline
- EMBASE
- The Cochrane Library
- Current Contents
- PreMedline
- Cinahl
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Cochrane Controlled Trials Register
- Health Technology Assessment (HTA) databases

The following search strategy was used to identify papers in Medline (Table 9). Similar search strategies were used for the other databases. The search strategies were validated by a researcher with expertise in searching the biomedical literature.

Table 9 Search strategy

Number	Search terms
1.	exp EPILEPSY, PARTIAL, MOTOR/ or exp EPILEPSY, TEMPORAL LOBE/ or exp EPILEPSY, COMPLEX PARTIAL/ or exp EPILEPSY, PARTIAL, SENSORY/ or exp EPILEPSY, REFLEX/ or exp EPILEPSY, TONIC-CLONIC/ or exp EPILEPSY, BENIGN NEONATAL/ or exp EPILEPSY, POST-TRAUMATIC/ or exp EPILEPSY, ABSENCE/ or exp EPILEPSY, FRONTAL LOBE/ or exp EPILEPSY/ or exp MYOCLONIC EPILEPSY, JUVENILE/ or exp EPILEPSY, ROLANDIC/ or exp EPILEPSY, GENERALIZED/
2.	exp Epilepsies, Partial/
3.	limit 2 to yr=1999
4.	exp Epilepsies, Myoclonic/
5.	limit 4 to yr=1999
6.	exp MYOCLONUS/
7.	limit 6 to yr=1999
8.	epilep\$.mp
9.	1 or 3 or 5 or 7 or 8
10.	exp Tomography, Emission-Computed/
11.	exp Gamma Cameras/
12.	positron emission tomography.mp
13.	(PET\$ or FDG\$).mp
14.	(18F or 18-F).mp
15.	or/10-14
16.	9 and 15
17.	Animals/
18.	Human/
19.	17 not (17 and 18)
20.	16 not 19
21.	Limit 20 to yr=1999 - 2004

In addition to the electronic database search the following HTA sites were searched (Table 10). The reference lists of retrieved HTA reports were scanned for any eligible articles that may not have been identified by the electronic database search.

Table 10 HTA sites searched

Organisation	Website
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.edu.ca/bcohta
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (US)	www.ohprp.state.or.us/ohrc
Minnesota Department of Health (US)	www.health.state.mn.us
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev
National Library of Medicine Health Service/Technology Assessment text (US)	http://text.nlm.nih.gov
NHS Health Technology Assessment (UK)	www.hta.nhsweb.nhs.uk
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca
Conseil d'Evaluation des Technologies de la Sante du Quebec (Canada)	www.cets.gouv.qc.ca
National Information Centre of Health Services Research and Health Care Technology (US)	www.nlm.nih.gov/nichsr/nichsr.html
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	www.stakes.fi/finohta/linkit/
Institute for Medical Technology Assessment (Netherlands)	www.bmg.eur.nl/imta/
AETS (Spain)	www.isciii.es/unidad/aet/cdoc.htm
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	www.anaes.fr
Institute for Clinical Systems Improvement (US)	www.icsi.org
Scottish Intercollegiate Guidelines Network (Scotland)	www.sign.ac.uk
Danish Centre for Evaluation and Health Technology Assessment (Denmark)	www.sst.dk

Eligibility of studies

The search identified 1719 non-duplicate citations (Figure 1). The eligibility criteria described in Table 11 were applied to the citations. A second reviewer applied the eligibility criteria in a blinded fashion to 516 citations (30%). There were four discrepancies (<1%) which were resolved by consensus. A total of 12 studies were considered eligible for inclusion in the review.

Data Extraction

Where possible, data was extracted from studies enrolling only the patient group of interest to the current assessment (ie patients with normal MRI or discordant MRI and EEG results). Studies that evaluated PET in both patients with structural lesions on MRI and concordant EEG and those without were also included if the results presented could be disaggregated to obtain data for MRI-normal or MRI/EEG-discordant patients alone. EEG and MRI results for each patient were used to identify data eligible for inclusion if the patient subgroup of interest was not clearly described by the investigators. This approach was chosen to allow the most inclusive use of all the available evidence. It relies on assumptions about the tabulated data that cannot be validated without additional information about the study patients. It is possible that some of the included patient data may not be fully representative of the patient group of interest. Errors of inclusion or exclusion may have occurred and are a potential source of bias.

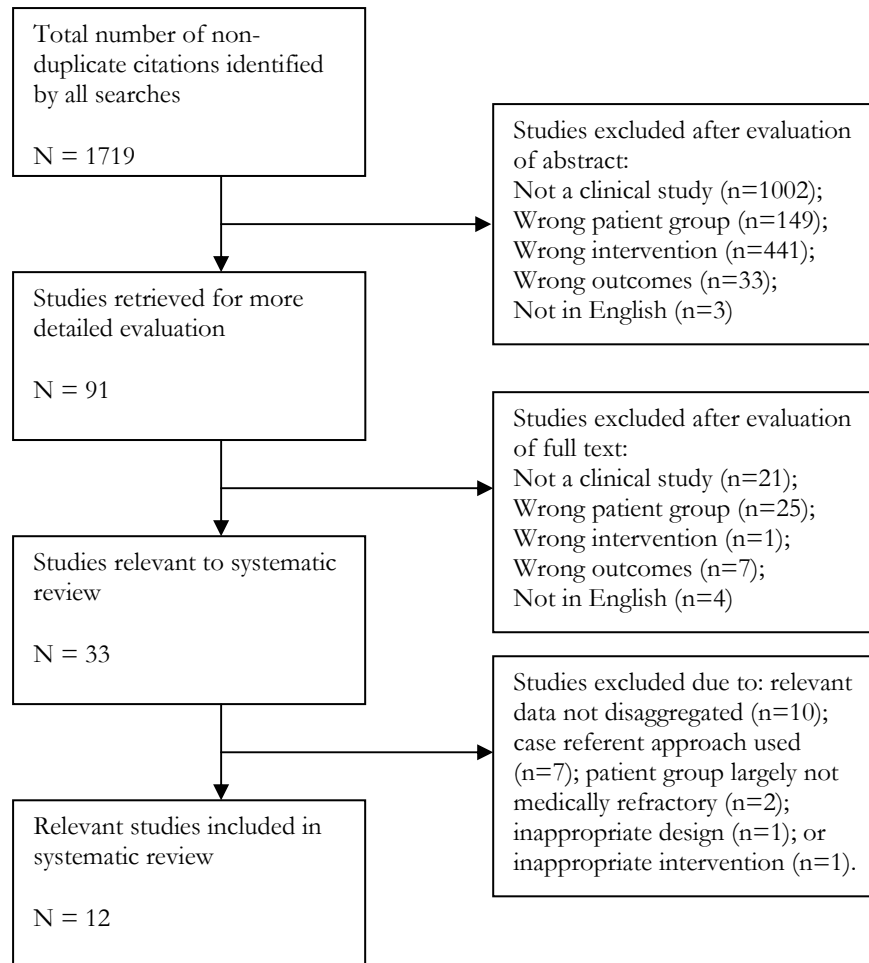


Figure 1 QUORUM flowchart of study inclusions and exclusions

Table 11 Study exclusion criteria

<p>1. Not a clinical study</p> <p>Reports excluded were those describing non-systematic reviews, case reports, case series of less than 10 patients, letters, editorials, animal, in-vitro and laboratory studies.</p> <p>2. Wrong patient group</p> <p>Studies were to include patients with:</p> <ul style="list-style-type: none">• epilepsy refractory to medical treatment being considered for surgery; and• prior tests performed including MRI and EEG that were insufficient to plan surgery. <p>3. Wrong intervention</p> <p>Studies were to use full-ring FDG-PET imaging.</p> <p>4. Wrong outcomes</p> <p>Studies had to report on at least one of the following:</p> <ul style="list-style-type: none">• diagnostic accuracy;• localisation rates;• change in clinical management;• changes in patient outcomes;• safety;• costs. <p>5. Not in English</p> <p>Due to time constraints, only studies published in English were eligible for inclusion unless they were deemed necessary to the review.</p>

Appraisal of the evidence

The evidence presented in the selected studies was assessed using the dimensions of evidence defined by the National Health and Medical Research Council (National Health and Medical Research Council 2000)

These dimensions consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. In this review, the strength of evidence is based on an assessment of the quality, applicability and statistical precision of the results of the included studies. The size of the effect and relevance of the evidence is determined using expert clinical input.

Quality and applicability

The quality of a study refers to the extent to which it has been designed and conducted to reduce bias in the estimation of the outcome. The potential sources of bias vary according to whether the study is designed to measure the impact of the test on health outcomes (where the ideal is a randomised trial of alternative tests) or to estimate the diagnostic accuracy of the test (for which the ideal is cross-sectional analytic studies of consecutive patients all followed up with a valid reference standard). Several tools that assess study quality are available, including a checklist for different study designs in the NHMRC handbook on how to conduct systematic reviews (National Health and Medical Research Council 2000). The levels of evidence designated by the NHMRC (Table 12) will be used to rank evidence included in the review from studies assessing the direct impact of PET on health outcomes. In contrast to the criteria used to assess the quality of controlled trials (Jadad 1996), checklists used to assess the quality of diagnostic test accuracy have not yet been validated (Jaeschke, Guyatt, & Sackett 1994; Bossuyt et al 2003; Whiting 2004). The checklist used in this review is the QUADAS tool (Table 13). This has recently been developed by experts in the field after consideration of the growing body of evidence relating to sources of bias and variation relevant to studies of diagnostic test accuracy (Whiting 2004).

The applicability of a study refers to the extent to which the study results are applicable to the intended use of the test in practice. The main sources of study variation that limit the applicability of the study results are related to the methods used to select the study population, in particular how representative the population is to the intended use of the test including the spectrum of disease sampled.

Table 12 Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from NHMRC, 1999.

Table 13 QUADAS tool

Was the spectrum of patients representative of the patients who will receive the test in practice?
Were selection criteria clearly described?
Is the reference standard likely to correctly classify the target condition?
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
Did patients receive the same reference standard regardless of the index test result?
Was the reference standard independent of the index test (ie the index test did not form part of the reference standard)?
Was the execution of the index test described in sufficient detail to permit replication of the test?
Was the execution of the reference standard described in sufficient detail to permit its replication?
Were the index test results interpreted without knowledge of the results of the reference standard?
Were the reference standard results interpreted without knowledge of the results of the index test?
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
Were uninterpretable/intermediate test results reported?
Were withdrawals from the study explained?

Of the 14 criteria listed in the QUADAS tool, the key factors regarding quality and applicability relevant to this review are described below:

1. The selection and application of the reference standard

In this review, surgical outcome is used as the reference standard in the absence of a ‘perfect’ test for correctly detecting the seizure focus when standard EEG and MRI are inconclusive. Surgical outcome was preferred over a composite of all possible testing (MRI, EEG, Wada, PET, SPECT, invasive EEG, video EEG) because only surgical outcome provides clinically relevant information about whether the seizure focus was correctly localised. In addition, the use of a composite reference standard that includes the index test will result in inflated estimates of accuracy (incorporation bias). Furthermore, it would be difficult to identify a group of studies that all used the same combination of tests.

Using surgical outcome as the reference standard, true positives are patients with a PET-defined seizure focus who achieve a good surgical outcome and false positives are patients with a PET-defined seizure focus who do not achieve a good surgical outcome. One problem with using surgical outcome as a reference standard is that it is based on the assumption that all patients with an informative PET scan will proceed to surgery. This is not likely to be the case, for example if PET correctly localised the seizure focus and surgery was not offered or was declined by the patient.

Surgical outcome is also an imperfect reference standard for patients with a negative PET result if it cannot be used to assess patients with uninformative PET findings (a source of partial verification bias). In settings where additional testing may be available, ‘true’ and ‘false’ negative results can only be estimated if patients with uninformative PET results go on to have invasive EEG.

The proportion of patients who achieved a positive outcome after surgery when the seizure focus was correctly localised by PET (test sensitivity) requires an estimation of these false negatives (patients with an uninformative PET who benefited from surgery following additional tests). In studies that do not include additional testing for PET

negative patients, an estimation of ‘true’ and ‘false’ negatives is not possible and the results are limited to an estimation of the proportion of patients with a PET-defined seizure focus who have a positive surgical outcome (positive predictive value). This estimation will be flawed because as described above it is likely that not all PET positive patients will proceed to surgery.

Due to these fundamental limitations of the reference standard, this review reports on evidence about the proportion of patients with a lesion localised by PET (diagnostic yield) as well as estimates of the rate of ‘correct localisation’ achieved by PET.

2. Selection of patients – spectrum bias

Ideally, studies of test accuracy prospectively and consecutively enrol all eligible patients. This method helps to avoid the selective enrolment of patients with characteristics that are not representative of the intended population of the test and that may bias the estimation of the accuracy of PET. This is referred to as spectrum bias. In this review, it was sometimes not clear to what extent prior testing was unhelpful in the patients enrolled. If many of these patients were eligible for surgery regardless of the PET result then the rates of localisation reported will not be generalisable to patients where prior testing is insufficient to plan surgery.

Expert advice

An advisory panel with expertise in the provision of clinical PET services, nuclear medicine, and neurology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC’s practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided at Appendix B.

Results of assessment

Is it safe?

It is generally accepted that positron emission tomography is a non-invasive and safe diagnostic procedure.

There is limited published information available on the safety of positron emission tomography. Safety issues are primarily discussed in terms of the safety of the positron-emitting radiopharmaceutical, rather than the safety of the procedure as a whole. Silberstein (1998) conducted a study of 22 PET centres in the United States to determine the prevalence of adverse reactions to positron-emitting radiopharmaceuticals. ^{18}F -fluorodeoxyglucose was the principle radiopharmaceutical used. The survey also reported on ^{11}C - CO_2 , ^{11}C -methionine, ^{13}N - NH_3 and ^{15}O - H_2O . The centres provided retrospective data for the time from opening of the centre to 1994 and prospective monthly data from 1994 to 1997. To 1994 33,925 radiopharmaceutical doses were administered, with an additional 47,876 doses being administered prospectively. A total of 81,801 doses of positron-emitting radiopharmaceuticals were reported in the survey. The authors report that there were no adverse reactions reported or observed to any of these 80,000 doses, with an upper 95% confidence limit of 3.7 per 100,000 doses.

From this large prospective study, it can be seen that the radiopharmaceuticals used for positron emission tomography have been well documented and appear to be safe. The United States Pharmacopoeia drug information for FDG also indicates that there are no known adverse effects associated with the use of FDG (USP DI 1998).

Radiotracers are generally used in microgram quantities, and as such the incidence of adverse reactions to very small amounts of labelled molecules are likely to continue to be low.

Patients undergoing a PET scan will be exposed to a certain amount of ionising radiation. It has been estimated that the radiation dose in a patient undergoing a FDG-PET scan (less than ten millisieverts) is comparable to the dose received during a diagnostic CT scan (Kneifel 2003).

None of the studies included in this assessment reported any adverse events associated with PET.

Is it effective?

Localisation

A total of 11 studies reported PET localisation or lateralisation of seizure focus in patients with medically refractory epilepsy and either normal MRI or nonconcordant MRI and EEG results. Table 14 lists these studies and describes the percentage of patients localised or lateralised by PET, along with the patient groups investigated, and the method of PET interpretation used. The included studies employed clinical case series designs. Five were retrospective with a consecutive series of patients recruited; one

was consecutive but did not describe the prospective or retrospective nature of the study; one was retrospective but did not state whether the study was consecutive; and four studies did not describe if patient recruitment was prospective or consecutive. Studies included both temporal and extratemporal lobe epilepsy patients, and both paediatric and adult populations were represented. The median percentage of localised or lateralised patients in the included studies was 70%, with a range of 39-100%.

With regard to the method of PET interpretation, the majority of studies used qualitative visual interpretation. However, no meaningful conclusions about the value of visual interpretation for localisation or lateralisation appear possible given the variation in lateralisation and localisation that was evident (range 36% to 90%). Despite this, several of the included studies suggest plausible results relating to visual interpretation in patients with different types of epilepsy. Two studies indicate that visual localisation and lateralisation rates are higher in temporal lobe patients than in extratemporal lobe patients (Meyer et al 2001; O'Brien et al 2001). One of these studies reports that this difference was highly statistically significant ($p < 0.0001$) (O'Brien et al 2001). Another small study reporting multiple methods of PET interpretation suggests that some quantitative methods (statistical parametric mapping, with $p < 0.005$; region of interest) may be superior to visual interpretation in extratemporal lobe patients (Plotkin et al 2003). However more studies with greater patient numbers are required before drawing firm conclusions based on these results.

Similarly, conclusions regarding quantitative methods of PET interpretation are difficult to make. It is plausible that statistical parametric mapping (SPM) using a p-value of 0.005 and region of interest (ROI) interpretations produce similar localisation rates, and that these rates are greater than those produced by SPM using a p-value of 0.001. Although no statistical comparison was conducted, the percentage of localised patients using ROI was similar in two studies, albeit higher in a sample of temporal lobe patients (Tatlidil et al 2000) than a sample of extratemporal patients (Plotkin et al 2003). The superiority of SPM ($p < 0.005$) over SPM ($p < 0.001$) makes intuitive sense, since the p-value relates to the threshold used to determine a difference in hypometabolism between patients being studied and normal controls. Hence, as the p-value decreases (ie threshold becomes higher), it becomes less likely that focal hypometabolism will be identified.

The localisation and lateralisation information presented here should be interpreted with caution due to a number of methodological limitations in the included studies. Firstly, it was not uncommon for studies to be conducted retrospectively (Hwang et al 2001; Kim et al 2000), for a non-consecutive patient group to be selected or for such details to be inadequately reported (Plotkin et al 2003; Tatlidil et al 2000). It has been noted that a consecutive enrolled, prospectively selected series of patients is the study design most likely to minimise selection bias in assessing diagnostic test accuracy (Knottnerus, Dinat, & van Schayk 2002).

In addition, the generally low sample sizes of the included studies compounds concerns about the representativeness of their target populations. Other interpretative issues associated with specific studies included the classification of some patients as “possibly” lateralised when the PET results were mild or bilateral with more pronounced hypometabolism on one side (Meyer et al 2001). Further, one study defined a localisation as an abnormality being “confined to one or two lobes” (Juhasz et al 2003), a less strict definition than was applied in other studies. In both cases, these patients were included in the lateralisation calculations presented here, thus possibly resulting in an overestimate. Also, one study included PET results in the battery of tests that were

nonconcordant in the presurgical evaluation (this is a slightly different patient group than those who have nonconcordant EEG and MRI findings only) (Salanova, Markand, & Worth 2001). The latter methodological difficulty may explain the low percentage of patients localised in this study.

Table 14 Lateralisation or localisation of seizure focus by PET in medically refractory epilepsy patients

Study	n	Epilepsy Type	PET Interpretation	Lateralisation/ Localisation % (95% CI)	Comments
Salanova, Markand, & Worth 2001	18	Temporal lobe epilepsy	Visual	38.8 (±22.5)	Pts with nonconcordant noninvasive results but PET included in this.
Hwang et al 2001	32	Neocortical epilepsy (temporal and extratemporal)	Visual	59.4 (±17.0)	“Correct” localisation (concordant with operative site and location of histopathologic abnormality). Cannot determine numbers of TLE/ETLE pts, but ETLE pts ≥ 50% of sample.
Juhasz et al 2003	19 3 16	Neocortical Temporal lobe Extra-temporal	Semiautomated software package	63.2 (±28.5) 66.6 (±53.4) 62.5 (±23.7)	Includes 3 temporal and 16 extratemporal lobe pts. Localisation defined as “confined to one or two lobes”.
Plotkin et al 2003	11	Extratemporal lobe epilepsy	SPM (p<0.005) ROI Visual SPM (p<0.001)	63.6 (±28.4) 63.6 (±28.4) 36.4 (±28.4) 9.1 (±17.0)	Frontal lobe pts.
Tattidil et al 2000	19	Temporal lobe epilepsy	ROI (asymmetry indices)	68.4 (±20.9)	
Meyer et al 2001	20 15 5	Partial seizures Temporal lobe Extratemporal	Visual	70.0 (±20.1) 93.3 (±12.6) 0.0 (±52.2)	Includes “possibly” lateralised pts. Includes 15 temporal and 5 extratemporal lobe pts.
Spanaki et al 1999	39	Temporal and extratemporal lobe epilepsy	Not described	74.4 (±13.7)	Cannot determine numbers of TLE/ETLE pts.
O'Brien et al 2001	55 41 14	Partial epilepsy Temporal lobe Extratemporal	Visual	76.0 (±11.3) 90.0 (±9.1) 36.0 (±25.1)	Includes 41 temporal and 14 extratemporal lobe pts.
Won et al 1999	20	Temporal and extratemporal lobe epilepsy	Not described	80.0 (±17.5)	“Correct” lateralisation (concordant with pathologic diagnosis). Cannot determine numbers of TLE/ETLE pts.
Murphy et al 2004	10 9 1	Partial epilepsy Temporal lobe Extratemporal	Software package.	100.0 (-30.8) 100.0 (-33.6) 100.0 (-97.5)	PET registered to MRI. 1 pt had combined PET/subdural electrode grids. Includes 9 temporal and 1 extratemporal (frontal) lobe pt.
Kim et al 2000	12	Temporal and extratemporal epilepsy	Not described	100.0 (-26.5)	PET “abnormality” assumed to equate to localisation. Cannot determine numbers of TLE/ETLE pts, but n(TLE pts) ≤ 2.

The studies are presented in ascending order of percentage of patients lateralised or localised. For studies that employ multiple methods of PET interpretation, the method with the highest lateralisation/localisation percentage is used for ranking purposes. For studies where temporal lobe and extratemporal lobe results could be extracted along with results for the whole sample, the percentage for the entire sample is used for ranking purposes.

Results for the majority of studies were obtained for simple lateralisation/localisation – that is, the percentage of patients for which a focal abnormality was lateralised or localised by PET, with no reference standard applied to determine whether the localisation was “correct” (accurate). There were two exceptions to this, whereby “correct” localisation was reported (ie concordance between PET localisation and pathological diagnosis, or pathological diagnosis and the surgical site) (Hwang et al 2001; Won et al 1999). For these studies, simple localisation could not be extracted. These studies are considered along with localisation results and not accuracy results since they

do not utilise the reference standard considered appropriate for this review (postsurgical outcome). However, it should be noted that they are likely to provide a conservative estimate of simple localisation, as defined by the parameters of this review, as they do not include PET localisations considered “false” against the reference standard.

Correct Localisation

A total of four studies reported correct PET localisation or lateralisation of seizure focus in patients with medically refractory epilepsy and either normal MRI or nonconcordant MRI and EEG results. Localisation or lateralisation was considered correct when verified against the reference standard of positive surgical outcome, with Engel’s class I or II considered positive, and class III or IV considered negative. When outcomes were not reported by Engel’s classification, seizure-freedom was considered positive, and other outcomes were considered negative. Table 15 lists the included studies and describes the percentage of patients correctly localised or lateralised by PET, along with the patient groups investigated, and the method of PET interpretation used. Studies employed clinical case series designs, with two being consecutive and retrospective, and two being unclear regarding the prospective or consecutive nature of the study. One study included only temporal lobe epilepsy patients, one included only extratemporal patients, and two studies included both temporal and extratemporal patients (one of these included only one extratemporal patient). Both paediatric and adult populations were represented. The median percentage of correctly localised or lateralised patients in the included studies was 80%, with a range of 62-100%.

Table 15 Correct lateralisation or localisation of seizure focus by PET, and proportion of PET positive patients with good outcomes in patients with medically refractory epilepsy

Study	n	Epilepsy Type	PET Interpretation	Correct Lateralisation/ Localisation % (95% CI)	PET positive with good outcomes % (95% CI)	Comments
Tattidil et al 2000	19	Temporal lobe epilepsy	ROI (asymmetry indices)	62.5 (±21.8)	38.5 (±21.9)	Outcomes classified as seizure-free, significantly improved (< 3 seizures per yr and 90% reduction), and not significantly improved.
Juhasz et al 2003	12	Extratemporal lobe epilepsy	Semiautomated software package	75.0 (±24.5)	85.7 (±19.8)	
Won et al 1999	13	Temporal and extratemporal lobe epilepsy	Visual	84.6 (±19.6)	- -	Unable to calculate proportion of PET+ pts with good outcome. Cannot determine numbers of TLE/ETLE pts.
Murphy et al 2004	10 9 1	Partial epilepsy <i>Temporal lobe</i> <i>Extratemporal</i>	Software package.	100.0 (-30.8) 100.0 (-33.6) 100.0 (-97.5)	100.0 (-30.8) 100.0 (-33.6) 100.0 (-97.5)	PET registered to MRI. 1 pt had combined PET/subdural electrode grids. Includes 9 temporal and 1 extratemporal (frontal) lobe pt. Outcomes classified by Engel’s class.

Additionally, Table 15 describes the proportion of patients for whom PET localised or lateralised a seizure focus and who had a positive post-surgical outcome. The median percentage of PET positive patients with good outcomes in the included studies was 86%, with a range of 38-100%.

It is difficult to compare the rates of correct localisation and positive clinical outcomes in PET positive patients reported here to those described in the previous MSAC evaluation of PET for epilepsy (Medicare Services Advisory Committee 2000). The previous assessment reported these characteristics from only two studies, and used a different reference standard (pre-surgical work-up) to that considered here. Despite these differences, that report concluded that the correct localisation (sensitivity) was high, in the range of 76-97% depending on the method of determining PET positivity. This is comparable to the results reported here, although a wider range was evident in this assessment. The previously reported range of positive outcomes for those with positive PET scans (positive predictive value: range 94-100%) is higher than that found here, although it must be stressed that these were derived from a small number of studies. The difference in results reported by the two assessments may be attributable to this, along with the different reference standards employed (postsurgical outcome is likely to be a more conservative reference standard than localisation obtained from the pre-surgical work-up).

It is noteworthy that one study included in the current assessment is responsible for the minimum values of both correct localisation and rate of positive outcomes for those patients who had a positive PET (Tatlidil et al 2000). This study reported patient outcomes as either seizure-freedom, significant improvement, or no significant improvement. Seizure-freedom was considered the appropriate classification of positive outcome in this case, however it is possible that some patients in the significant improvement category may meet the definition of Engel's class I or II. The values obtained from this study are therefore likely to be underestimates.

Limitations

The accuracy results from the studies described above are limited by methodological concerns relating to the reference standard. Firstly, if patients with a positive PET result are more likely to undergo surgery, then the reported correct localisation will be inflated close to 100%. Not all cases amenable to surgery who are PET negative are included in the study, and hence they are not in the denominator. This is known as partial verification bias, and will also lead to an underestimate of specificity in predicting poor surgical outcomes. Furthermore, all of the included studies selected patients who had undergone surgery and did not report information on patients who underwent presurgical work-up but were not operated on. This would include patients who may have had a negative result if they had undergone a PET scan. The result of this omission is that the true negatives are missing from the diagnostic accuracy equation. Due to these limitations, this assessment has not described test specificity or negative predictive value.

Further complicating the interpretation of these results is the issue of possible spectrum bias. Spectrum bias refers to the inclusion of an unrepresentative sample of patients in the study, such that the accuracy results may not be widely transferable (Greenhalgh 1997). This form of study bias particularly includes the spectrum of disease severity, since test sensitivity may vary based on this, but may also refer to patient characteristics such as age and gender. The potential for spectrum bias exists when the patient inclusion criteria are not explicitly reported. With reference to the current assessment, the nature of patient enrolment could not be determined for two of the six studies (Juhász et al 2003; Tatlidil et al 2000). Hence, it is possible that spectrum bias exists, and the transferability of accuracy results may be limited.

Seizure Outcomes

A total of 9 studies reported a primary outcome of postsurgical seizure control outcomes in the patient group of interest. Table 16 lists these studies and describes the percentage of patients in each with a positive postsurgical seizure outcome. The included studies employed clinical case series designs. Four studies were retrospective with consecutive patient recruitment; one was retrospective but did not state whether the study used consecutive patient recruitment; and the prospective or consecutive nature of patient recruitment could not be determined in four studies. The majority of studies reported outcomes in terms of Engel's classifications, and for these studies a positive outcome was defined as either Class I or Class II. In some instances only Class I results were available. For other studies, Engel's classification was not used and instead "seizure-freedom" was reported.

Table 16 Positive seizure control outcomes for studies using PET in the pre-surgical evaluation for medically refractory epilepsy patients

Study	n	Epilepsy Type	Follow-up	Engel's I or II % (95% CI)	Comments
Kim et al 2000	14	Temporal and extratemporal lobe epilepsy	≥1 yr	28.6 (±23.7)	Includes 2 patients who did not have PET. Only 2 pts with temporal lobe epilepsy.
Tatildil et al 2000	19	Temporal lobe epilepsy	1-5 yrs	42.1 (±22.2)	"Seizure-free" patients (not reported as Engel's class outcomes).
Hwang et al 2001	36	Neocortical epilepsy (temporal and extratemporal)	Mean of 34 mo (range 12-67)	61.1 (±15.9)	Includes 16 temporal and 20 extratemporal (11 frontal, 9 occipital) lobe epilepsy pts.
Won et al 1999	26	Temporal and extratemporal lobe epilepsy	Mean of 24 mo (range 12-35)	65.5 (±18.3)	Includes 6 patients who did not have PET. Includes 14 temporal and 12 extratemporal (7 frontal, 3 occipital, 2 multifocal) lobe epilepsy pts.
Juhasz et al 2003	12	Extratemporal lobe epilepsy	Mean of 17.2 mo (range 2-40)	67.0 (±26.6)	
Salanova, Markand, & Worth 2001	6	Temporal lobe epilepsy	Range of 2-8 yrs	67.0 (±37.6)	"Seizure-free" patients (not reported as Engel's class outcomes). Included as n=18 for localisation results.
Juhasz et al 2000	12	Neocortical epilepsy (temporal and extratemporal)	Mean of 15.3 mo (±5.3)	75.0 (±24.5)	Includes 3 temporal and 9 extratemporal (5 frontal, 3 central, 1 multifocal) lobe epilepsy pts.
O'Brien et al 2001	24	Temporal and extratemporal lobe epilepsy	Median of 17 mo (range 6-42)	91.7 (±11.0)	Only 2 pts with extratemporal lobe epilepsy.
Murphy et al 2004	10	Temporal and extratemporal lobe epilepsy	Mean of 26 mo (range 14-41)	100.0 (±23.7)	Only 1 pt with extratemporal (frontal) lobe epilepsy.

The median percentage of patients with a positive postsurgical outcome in the included studies was 67%, with a range of 29-100%. In general, it was apparent that the higher the proportion of extratemporal lobe patients included in the sample, the lower the proportion of reported Engel's class I or II/seizure-free outcomes, although statistical testing was not performed. This finding is consistent with international survey data suggestive of less favourable postsurgical outcomes in extratemporal compared with temporal lobe patients in general epilepsy populations (Engel 1996).

One included study reported multivariate analyses that evaluated the association between imaging tests (including PET) and surgical outcome (O'Brien et al 2001). It has been noted that such analyses may produce overly optimistic results that may not be reproducible in clinical practice or in similar study populations (Knottnerus & Muris 2002). Such results require external validation from well designed, independent studies in similar clinical populations. As such, these multivariate analyses have not been addressed in the current review.

The interpretation of the available outcome results is problematic in a number of ways. Firstly, as implied above, the definition of “positive” postsurgical seizure control outcomes varies from study to study. Several papers are consistent in their application of Engel’s classification system in reporting these outcomes. However, there are some included studies that do not report outcomes according to Engel’s classification, but rather report percentages of seizure-free and non-seizure-free patients (Salanova, Markand, & Worth 2001; Tatlidil et al 2000). “Seizure-free” patients in these studies may not be directly analogous to an Engel’s Class I outcome from other studies, since a Class I outcome whilst being labelled “free of disabling seizures” does in fact allow for some seizures to occur. Therefore, considering only results of seizure-freedom these studies would likely underestimate the proportion of patients with “positive” postsurgical seizure outcomes.

Another concern relates to the variable length of post-surgical follow-up evident in the included studies. At least three studies included patients with a follow-up of less than one year (Juhasz et al 2000; Juhasz et al 2003; O'Brien et al 2001), while some studies reported a range of follow-up times that extended to 5 years or beyond (Hwang et al 2001; Salanova, Markand, & Worth 2001; Tatlidil et al 2000). Shorter follow-up lengths are problematic for various reasons; for instance, several of the definitions used in the Engel’s classification system require observation for at least 2 years. Furthermore, it is difficult to compare results from studies with differing follow-up since post-surgical seizure control may fluctuate over time (Pilcher 2004).

Another issue complicating interpretation of these results is that in some cases it appeared that although PET was conducted, it did not contribute to surgical decision making (Hwang et al 2001; Won et al 1999). In such cases it is therefore not possible to attribute the post-surgical outcomes to the inclusion of PET results in the work-up. Other specific methodological and reporting difficulties also exist in the included studies. Among them are the inclusion of patients in outcome reporting who did not have PET in the pre-surgical evaluation (Kim et al 2000; Won et al 1999), and low patient numbers in general. In one study, the number of patients for which outcomes were reported was insufficient to meet inclusion criteria in the review. However this study was included because the surgical outcomes were presented for a subset of a larger group of patients which were eligible for localisation data extraction (Salanova, Markand, & Worth 2001).

Furthermore, it should be noted that non-randomised studies have a number of methodological limitations that render their results difficult to interpret. It has been noted that case series designs using consecutive patients are ideal for the assessment of diagnostic accuracy, however the impact of diagnostic tests on patient outcomes is best established by randomised controlled trials (Glaziou et al 2001). No randomised controlled trial evidence was available, and instead results are presented from Level IV evidence of generally poor quality. However, the median percentage of patients with a positive postsurgical outcome of 67% (range 29-100%) apparent here appears comparable with that reported in a comprehensive review of postsurgical outcomes for

medically refractory epilepsy patients in general (median 70%, range 33-93%) (McIntosh, Wilson, & Berkovic 2001). Again, there are difficulties in making such comparisons, most notably the fact that Engel's Class I or II was used (when possible) to define positive outcome in the present review, while McIntosh et al were primarily concerned with "seizure-free" outcomes.

Change in Management

Rationale for change in clinical management

Change in patient management can be considered in two ways. First, is there a solid rationale for a change in management based on the evidence of altered diagnosis together with evidence that different treatments are more or less effective for the conditions detected? This is evidence of diagnostic efficacy (Fryback & Thornbury 1991). Secondly, is there evidence that management is actually altered in practice based on the test results? This has been referred to as therapeutic efficacy (Fryback & Thornbury 1991).

Impact of FDG PET on clinical management

Evidence of change in clinical management due to the information provided by PET was only addressed by one study in the patient group of interest (O'Brien et al 2001). In this study, change in management was assessed retrospectively in 55 consecutive patients with medically refractory partial epilepsy, for whom previous non-invasive tests (notably EEG and MRI) had not provided sufficient localisation to proceed to surgery. The impact of PET was assessed as "high" if seizures were unlocalised prior to PET, and the PET findings allowed further evaluation for epilepsy surgery. Impact was considered "moderate" if localisation information was available from other modalities, but PET findings increased the confidence in localisation and enabled surgery to be offered. "Low" impact was demonstrated if other invasive tests were localising and PET was confirmatory but did not significantly alter management decisions. If PET results conflicted with other localising information they were considered "contradictory". Impact on management was judged to be "high" in 22 patients (45%), "moderate" in 7 (13%), and "low" in 23 (42%). No "contradictory" results were reported.

It is acknowledged that the study inclusion criteria were not strictly enforced in this instance (O'Brien et al 2001), raising concerns regarding the direct applicability of the sample to the patient group of interest to this review. There exists the possibility that the degree of "moderate" or "low" management change is inflated, due to the likely inclusion of patients for whom localisation was available from other tests. Furthermore, the design of this study was a retrospective case series, and as such the design is sub-optimal for the assessment of impact of diagnostic tests on clinical management. Changes in the diagnostic assessment and in the clinical management of patients cannot be reliably reconstructed post-hoc (Knottnerus, Dinat, & van Schayk 2002). These results are based on the assumption that the retrospective assessment truly reflected clinical interpretation prior to the PET. Change in clinical management is best established by randomised controlled trials (Glaziou et al 2001). However, while randomised evidence on a sufficient number of representative patients is preferable, this may not be possible for all diagnostic tests. In such situations, it is legitimate to draw conclusions from the data in the presence of evidence of diagnostic accuracy, coupled with available evidence of changes in management and evidence of the effectiveness of the interventions.

Conclusions

The ideal evidence for the demonstration of the impact of diagnostic tests on clinical management and outcomes comes from randomised controlled trials. The ideal evidence for the demonstration of diagnostic test localisation and accuracy involves large, prospective, consecutively enrolled diagnostic case series studies (Knottnerus, Dinat, & van Schayk 2002). For this assessment of PET in medically refractory epilepsy patients for whom MRI and EEG had not been able to localise a seizure focus, there were no studies representing the ideal evidence for any of localisation, accuracy, management change or outcomes. Since the initial MSAC assessment, a number of small case series studies investigating PET localisation and surgical outcomes in the population of interest, and change in management following PET have been published. A controlled trial of the effectiveness of surgery in a broader population of all patients with medically refractory epilepsy has also been published since the initial MSAC review. Thus, in assessing the value of PET in this review, the issue becomes whether it is appropriate to link the available evidence for localisation/accuracy to that for management change and outcomes.

Evidence for localisation (diagnostic yield) is drawn from 11 case series studies of generally low quality. Eight of these studies included 20 patients or less, and all included studies were either of retrospective or indeterminate design. For five studies it was unclear whether a consecutive series of patients was included. Individual studies also contained specific methodological difficulties which reduce the confidence that can be placed in the results (for example, differences in the definition of PET positivity, differences in the definition of nonconcordance in the presurgical work-up, and the application of a reference standard in reporting localisation results). The median localisation of these studies (70%; range 39-100%) therefore should be interpreted with caution; however it is clear that PET does provide some localising information for some patients. The evidence is suggestive that localisation is greater for temporal lobe lesions than for extratemporal lobe lesions, especially when PET is assessed visually. Defining the exact group of patients for whom PET is likely to provide extra localisation information is beyond the scope of the evidence at the present time.

Likewise, the evidence for diagnostic accuracy with the reference standard of post-surgical outcome is scant and problematic. Sensitivity and negative predictive value are not addressed due to methodological constraints inherent in the reference standard resulting in the reduction (or absence) of true and false negatives. Furthermore, this uncertainty regarding true negative values makes inferences about sensitivity problematic. It has also been noted that, due to the asymmetrical nature of accuracy characteristics of diagnostic tests, conclusions regarding sensitivity are unhelpful in the absence of information on specificity (Deville & Buntinx 2002). For this reason, the present assessment has presented accuracy in terms of correct localisation, and proportions of patients with positive PET scans and good outcomes. From the four included studies, the median percentage of correctly localised or lateralised patients was 80% (range 62-100%). However, the caveats applied to the interpretation of localisation results are also relevant here. Not only are the studies small (all reported less than 20 patients), all were retrospective or indeterminate in this aspect of study design, and two reported no information regarding the (non)consecutive nature of patient enrolment. There were also problems relating to different classifications of positive outcomes across studies. Partial verification bias and spectrum bias were also likely in the included studies, the former plausibly inflating the estimates of correct localisation reported, and the latter reducing their general applicability.

Evidence relating to post-surgical seizure-control outcomes was derived from 8 case series studies. Five of these studies enrolled 20 patients or less that met the criteria for inclusion in this review, all were retrospective or indeterminate in this aspect of study design, and four reported no information regarding the (non)consecutive nature of patient enrolment. However, the largest study (n=36) enrolled patients consecutively, contained similar number of temporal and extratemporal lobe patients, and represents the highest quality study available (Hwang et al 2001). This study reported positive seizure control outcomes in 61% of patients. This approximates the observed median of 67%, with positive seizure control outcomes ranging from 29% to 100%. It is therefore reasonable to conclude that some patients will have improved seizure control after having a pre-surgical evaluation that includes PET. The size of this effect compared to patients who do not proceed to surgery cannot be estimated without data from controlled studies. The available data suggests that post-surgical outcome may be better in patients with temporal lobe lesions compared with patients with extratemporal lobe lesions. This is consistent with large survey reports in general epilepsy populations (Engel 1996).

The evidence for management change based on PET results is restricted to a single, retrospective, consecutively enrolled case series study (O'Brien et al 2001). PET's impact on management was judged to be "high" in 45%, "moderate" in 13%, and "low" in 42% of patients, although failure to strictly enforce study eligibility criteria creates uncertainty about this study's direct applicability to the patient group of interest here. Despite these limitations, this study supports the theoretical possibility that PET alters clinical management.

The evidence summarised above is problematic. However, given that randomised controlled studies may not ever be feasible to undertake due to the small patient numbers involved, a strategy of linking the available evidence of diagnostic yield, accuracy and therapeutic effectiveness, combined with evidence of the effectiveness of epilepsy surgery is justified. Surgery for epilepsy has an established evidence base regarding its effectiveness in reducing or controlling medically refractory seizures (McIntosh, Wilson, & Berkovic 2001), particularly for temporal lobe patients where randomised, controlled evidence has demonstrated the efficacy of surgery compared with medical management (Wiebe et al 2001). However, this evidence is based on a population with structural foci detected by EEG and MRI, as opposed to patients with functional foci from PET and insufficient information from EEG and MRI. Thus, any conclusions made by linking the evidence of extra localisation data provided by PET to improved surgical outcomes assume firstly that the efficacy of surgery is equivalent in patients with structural and functional foci, and secondly that PET does in fact result in altered management. If, based on current clinical expertise these assumptions are judged to be reasonable, then it may be concluded that PET provides extra localisation information in some patients with medically refractory epilepsy, in whom MRI and EEG had not been able to localise a seizure focus, and that some of these patients will have good post-surgical seizure control outcomes. There is insufficient evidence to determine the size of this effect.

What are the economic considerations?

This section provides a best estimate of potential costs for PET to the health system in comparison with medical management for medically refractory epilepsy patients in whom MRI and EEG have failed to localise a structural lesion. As outlined in the previous section, evidence available for this group of patients is currently limited and hence only a

partial cost analysis has been undertaken. Whilst this analysis is subject to constraints, it provides an indication of plausible costs and therefore is still relevant to this review.

The costs indicated in this analysis relate to costs incurred by the health system. Indirect costs such as patient-incurred expenses or indeed welfare payments to patients unable to work due to medically refractory epilepsy are not incorporated.

Limitations of the cost data

No published Australian cost-effectiveness or cost studies of PET in medically refractory epilepsy patients with no focus on conventional imaging were identified. However, ongoing research to estimate Australian costs for the medical and surgical management of medically refractory epilepsy was identified (unpublished data provided by Professor Michael Murphy, September 2004). This data provides an estimated cost of:

- standard medical management including costs of medication, medical services and routine pathology; and
- surgery including costs for the pre, peri and post-operative periods

The cost analysis also includes an estimate of:

- the 'real' cost of a PET scan (including capital costs); and
- the proportion of patients proceeding to surgery after a successful PET scan, provided by clinical experts on the advisory panel.

Cost analysis methods

The purpose of this analysis is to estimate an indicative baseline case for the costs of PET as a treatment strategy relative to conventional medication given best available current evidence of test accuracy, treatment effects and resource use associated with treatment. This baseline case should however be seen as indicative given current uncertainty about each of these factors. Uncertainty is considered in sensitivity analyses and threshold analyses examining potential conditions under which PET could be cost saving.

The baseline analysis assessed the expected cost of treatment following PET for patients presenting with medically refractory epilepsy, compared with expected cost for treatment without PET (the cost of conventional medication) over a 10-year period. The expected cost for PET was calculated by examining the likelihood the PET scan would localize lesions, the likelihood patients would then proceed to surgery and the likelihood that surgery would then be successful. The decision tree in Figure 2 indicates the various outcomes that may occur. The costs associated with these different paths multiplied by the chance of them occurring gave rise to an overall expected cost for treatment of patients following a PET scan. This was compared to the cost of conventional medication (calculated as the cost of conventional medication over 10 years and discounted at 5%).

Assumptions about the proportion of patients localised by PET, those proceeding to surgery after a localising PET, and those with positive seizure control outcomes post-surgery are detailed in Table 17. The estimated costs of PET, surgery, and annual medical management costs per patient (for non-surgical patients, successful and non-successful

surgical patients) are also described. A discount factor of 5% has been applied to costs of medical management. These base case estimates were varied in a one-way sensitivity analysis. In undertaking this costing, it has been assumed that patients with poor post-surgical seizure control outcomes (ie unsuccessful surgery) will incur conventional medication costs, but will have no additional costs associated with treatment of unsuccessful surgery. These assumptions used are listed in Table 17.

Table 17 Assumptions used in cost analysis

Variable	Base case	Sensitivity analysis
% patients localised by PET	70%	39 – 100%
% localised patients proceeding to surgery	75%	30 – 100%
% successful surgery	67%	29 – 100%
Cost of PET per patient	\$1,500	\$750 - \$3,000
Cost of surgery per patient	\$19,500	\$15,600 - \$23,400
Cost of medical management (no surgery, or unsuccessful surgery ¹) per patient per year	\$5,600	\$2,800 - \$11,200
Cost of medical management after successful surgery per patient per year	\$600	
Discount applied to cost of medical management ²	5%	3 – 8%

¹ Patients with unsuccessful surgery assumed to incur conventional medication costs (ie no additional costs for treatment of unsuccessful surgery).

² PET and surgery costs assumed to be incurred in the present year hence no discount applied.

Cost of PET compared with medical management

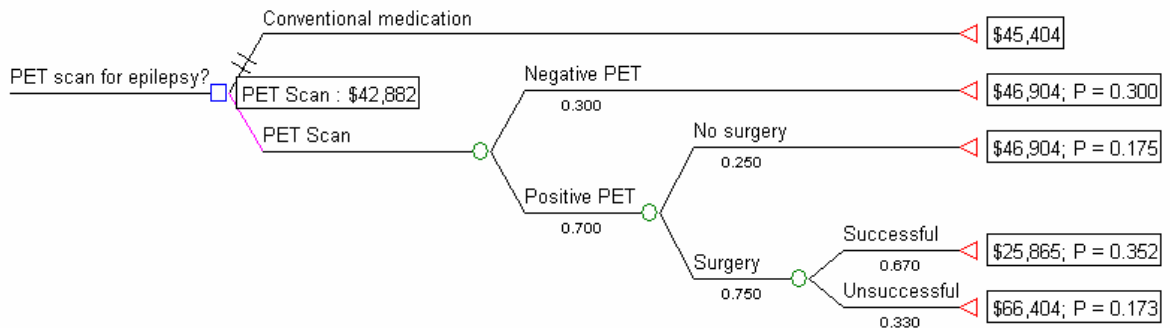
Based on the available data, using a PET scan as a part of a diagnostic appraisal has a higher expected cost (\$29,200 per patient) at 5 years than medical care where PET was not used as part of the diagnostic approach where a patient would receive medical management alone (\$25,457 per patient), a difference of \$3,742. The threshold where PET has a lower expected cost than conventional medication is at 8 years; however this threshold figure is not robust to sensitivity analyses. At 10 years, the PET group has a lower expected cost (\$42,882 per patient) than 10 years of medical management (\$45,404 per patient), a difference of -\$2,522 (see Figure 2). Therefore, based on cost information only, using PET as part of a diagnostic approach is expected to be cost saving in the long term.

All costs included in this model are based on costing data from one Australian tertiary institution, hence one way sensitivity analyses (varying one factor at a time) were conducted. Using a 10 year base model and one way sensitivity analyses (varying one factor at a time) this choice can be shown to be robust to:-

- Variations in discount factors (base = 5%, varied between 3% and 8%)
- Variations within the expected range of positive PET scans (base = 70%, varied between 39% and 100%)
- Variations to patients proceeding to surgery post PET scans (base = 75%, varied between 30% and 80%)
- Variations in the cost of PET (base = \$1500, varied between \$750 and \$3000)
- Variations in the cost of surgery (base = \$19,500, varied between \$15,600 and \$23,400)

This means that even at the extreme of these ranges, including PET in the diagnostic approach would still have a lower expected cost than conventional medication.

Figure 2 Decision tree comparing costs of PET and medical management, 10-year base model



The difference in expected costs is sensitive to:

- Changes in the probability of successful surgery. Base = 67% (range 29-100%). At 29% probability of successful surgery PET has a higher expected cost. The threshold is approximately 56%; so if 56% or more of patients undergoing surgery experience a reduction in seizures, PET would have the lower expected cost at 10 years. If less than 56% having surgery experience a reduction in seizures, and given the other assumptions made, conventional medical treatment has the lowest expected cost at 10 years.
- Changes to the cost of conventional medication and medical care. Base = \$5,600 (range varied by factors of 0.5 and 2 = \$2,800-\$11,200). The lower range of \$2800 resulted in PET yielding a higher expected cost. The threshold is approximately \$4,750; so if conventional medical care costs more than \$4,750 per annum per patient, PET yields a lower expected cost.

It should also be noted that the analyses presented above are costings only, and do not take into account health and social benefits that the technology may provide. In addition this analysis only takes into account costs up to 10 years. Any costs saved by PET at 10 years would be likely to further increase over time.

Conclusions

Safety

It is generally accepted that PET is a noninvasive and safe diagnostic procedure. Safety issues are primarily discussed in terms of the safety of the positron-emitting radiopharmaceutical, rather than the safety of the procedure as a whole.

In a large study of 22 FDG PET centres in the United States no adverse reactions to positron-emitting radiopharmaceuticals were reported for 33,925 retrospective doses of positron-emitting radiopharmaceuticals from before 1994 or 47,876 prospective doses from 1994 to 1997.

The United States Pharmacopoeia drug information for FDG also indicates that there are no known adverse effects associated with the use of FDG. In addition, radiotracers are generally used in microgram quantities, and as such the incidence of adverse reactions to very small amounts of labelled molecules are likely to continue to be low.

Patients undergoing a PET scan will be exposed to a certain amount of ionising radiation. It has been estimated that the radiation dose in a patient undergoing a FDG-PET scan (less than ten millisieverts) is on par with that received during a diagnostic CT scan.

Effectiveness

In patients where PET localises a seizure focus, the potential benefit of PET lies in this information leading to active management, with surgery resulting in improved patient outcomes. This review did not identify evidence from controlled trials about the effectiveness of PET in patients for whom EEG and MRI results are insufficient to proceed to surgery. Evidence from case series suggests that PET provides localisation information in some patients, and that some patients have good post-surgical outcomes after having a PET scan in their presurgical workup (Level IV evidence). The accuracy of PET in this patient group cannot be estimated due to problems defining a reference standard. A single study (Level IV) investigating the impact of PET on clinical management suggests that PET is promising in this regard. Attempts to link the evidence of extra localisation data provided by PET to improved surgical outcomes assume firstly that the efficacy of surgery is equivalent in patients with structural and functional foci, and secondly that PET results in altered management. If, based on current clinical expertise these assumptions are judged to be reasonable, then it may be concluded that PET provides extra localisation information in some patients with medically refractory epilepsy, in whom MRI and EEG had not been able to localise a seizure focus, and that some of these patients will have good post-surgical seizure control outcomes. There is insufficient evidence to determine the size of this effect.

Cost-effectiveness

A simple cost analysis suggests that the use of PET in the patient population of interest may be cost saving in the long term. However, the potential for PET to be cost saving relative to conventional care was sensitive to the probability of successful surgery and the cost of conventional care. While in the baseline case with 67% percent probability of successful surgery PET had an expected cost saving of \$2,522 per patient, this reduced to 0 at a threshold probability of successful surgery of 56%. Similarly, no cost saving of PET was observed if the costs of conventional care were estimated at lower than \$4,750 per year. Ranges of uncertainty for variables related to cost of PET and the cost of surgery did not reduce the baseline cost saving from PET to 0, but can be seen as important in combination with this treatment uncertainty.

This analysis does not take into account the potential health benefits provided by the technology, nor the broader potential benefits of improved health such as patients returning to work. Further evidence regarding the clinical effectiveness of PET, quality of life outcomes and the costs of medical and surgical care is required before a formal cost-effectiveness analysis can be conducted.

Recommendation

In relation to positron emission tomography prior to surgery in patients with refractory epilepsy, where there is no focus with concordant results on usual structural imaging and electroencephalogram, this assessment finds the technology:

- is safe;
- provides additional localising information in some patients, for whom a proportion will have good post-surgical outcomes as a consequence; and
- is likely to be cost-effective in the long term.

MSAC recommends that public funding should be supported.

- The Minister for Health and Ageing accepted this recommendation on 2 March 2005.

Appendix A MSAC terms of reference and membership

The MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Rosemary Huxtable	Department of Health and Ageing
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Professor Alan Lopez	medical statistics and population health
Dr Ewa Piejko	general practice

Ms Sheila Rimmer

consumer health issues

Professor Jeffrey Robinson

obstetrics and gynaecology

Professor Michael Solomon

colorectal surgery, clinical epidemiology

Professor Ken Thomson

radiology

Dr Douglas Travis

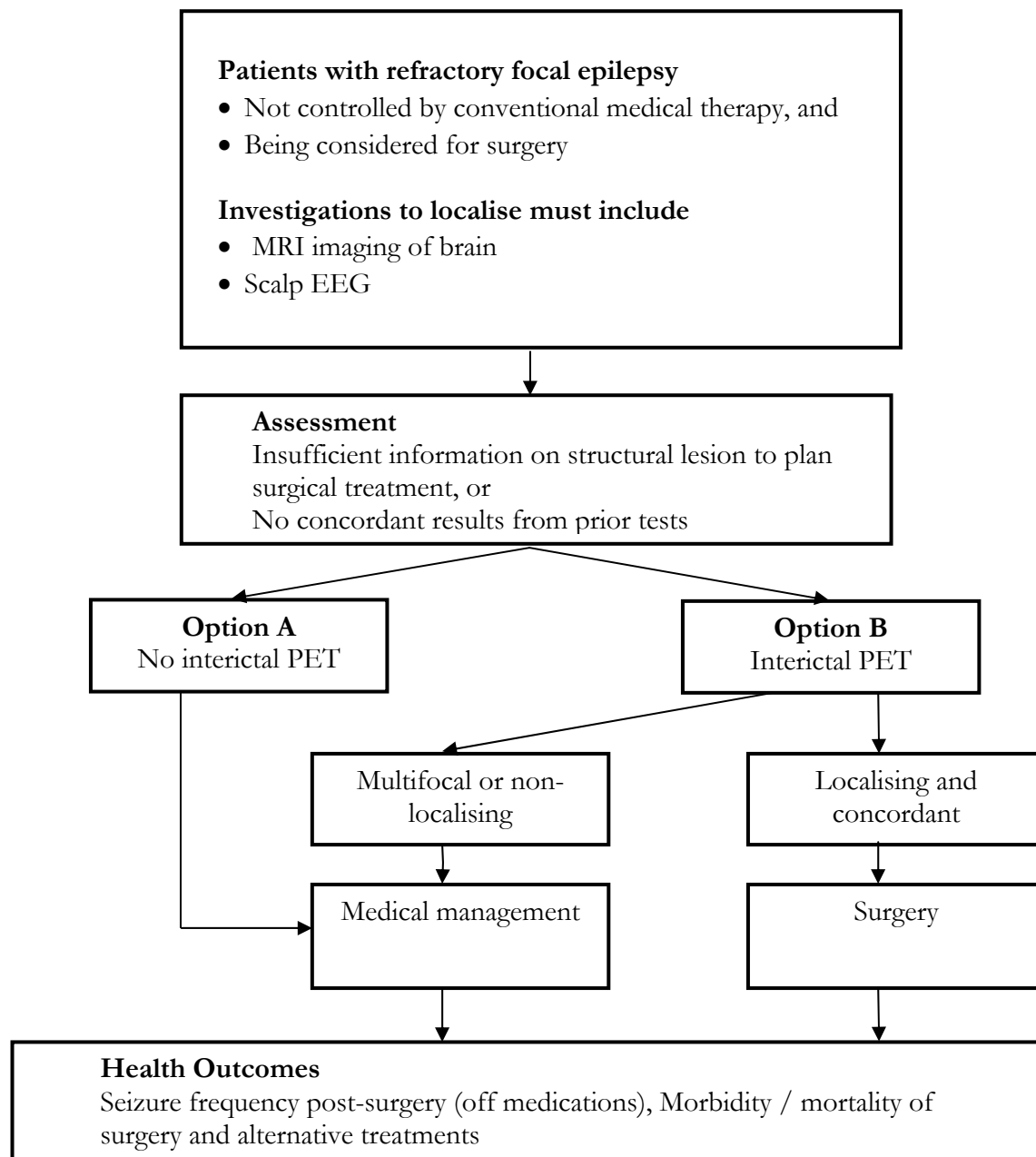
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Appendix B Advisory panel

Advisory panel for MSAC reference 26 Positron emission tomography (PET) for epilepsy

Professor Richard King (Chair) MBBS FRACP Program Director Medicine Southern Health, Monash Medical Centre East Bentleigh, VIC	Member of MSAC Physician
Professor Brendon Kearney MBBS FRACP FRACMA Executive Director Clinical Systems SA Department of Human Services Adelaide, SA	Member of MSAC Health Administrator
Professor John Simes MD SM FRACP Director NH&MRC Clinical Trials Centre Camperdown, NSW	Member of MSAC
Associate Professor Christopher Rowe MD FRACP Department of Nuclear Medicine and Centre for PET Austin Hospital Heidelberg, VIC	Nominated by the Australian and New Zealand Association of Physicians in Nuclear Medicine
Professor Michael Murphy MD FRACS Department of Neurosurgery St Vincent's Hospital Fitzroy, VIC	Nominated by the Neurological Society of Australasia/Royal Australasian College of Surgeons
Prof David Reutens MBBS MD FRACP Monash Medical Centre Clayton, VIC	Nominated by the Royal Australian College of Physicians
Ms Margaret Charlton Independent Consumer Representative Marion, SA	Nominated by the Consumers' Health Forum of Australia

Appendix C Clinical Flowchart



Appendix D Studies included in the review

The following tables outline the characteristics and results of the non-controlled studies included in this report.

Non-controlled evidence for PET in patients with epilepsy

Study	Type of study	N	Patient source and selection	Study design	Patient characteristics	Comparator	Reference Standard	Results	Comment
(Kim et al 2000)	Localisation and outcomes (level IV)	38	<p>Pts who underwent surgery for medically intractable epilepsy at the Division of Paediatric Neurosurgery, Seoul National University Children's Hospital between August 1993 and March 1998.</p> <p>Not stated whether pts were consecutive.</p> <p>Pts with brain tumours included if seizures intractable.</p> <p>Pts with <1yr follow-up post-surgery excluded.</p>	<p>Incremental value of FDG-PET. Retrospective.</p> <p>Presurgical evaluation consisted of interictal EEG and MRI in all pts. Video EEG was performed in 34 pts, PET in 30 pts, interictal SPECT in 19 pts, and ictal SPECT in 30. Subdural (n=24) or depth (n=25) EEG conducted on pts not localised by video EEG. Epileptogenic region localised by extraoperative (n=21) and intraoperative (n=2) ECoG. Cortical functional map of eloquent motor or language cortex obtained in 5 pts. IAP performed in 10 pts.</p>	<p>23M, 15F.</p> <p>Mean age at surgery 9.9 years (range 8mo-18yrs).</p> <p>12 patients met review inclusion criteria (normal MRI plus PET scan), 2 or fewer pts had TLE (unable to determine exact proportion).</p>	MRI, SPECT, neuropsych testing.	–	<p>12 pts (100%, 95% CI \pm 26.5%) with normal MRI had abnormal PET scans. "Abnormality" is assumed to be equivalent to localisation, but this is not explicitly stated.</p> <p>Outcomes assessed for 14 pts with normal MRI (no lesion or non-specific findings). 4 pts (28.6%, 95% CI \pm 22.5%) achieved favourable outcome (Engels Class I or II), including 0/2 (0.0%) temporal and 3/7 (42.9%) extratemporal resections.</p>	<p>Of the 14 pts with normal MRI and outcomes reported, there are 2 pts for whom PET was not conducted, and hence for whom PET did not contribute to pre-surgical evaluation.</p> <p>Patients may overlap with Hwang, Kim et al 2001, and Won, Chang et al 1999.</p>
(Hwang et al 2001)	Localisation and outcomes (level IV)	117	<p>Consecutive pts who underwent surgery for medically intractable, pathologically confirmed neocortical epilepsy between October 1994 and October 1998.</p>	<p>Incremental value of FDG-PET. Retrospective.</p> <p>Presurgical evaluation consisted of video EEG, MRI and neuropsych studies in all pts. 103 pts had PET, 93 had interictal SPECT, 91 had ictal SPECT, and 86 with normal MRI or nonconcordant imaging had intracranial EEG.</p> <p>PET scans underwent qualitative visual interpretation, with blinding to other tests. The area of greatest decrease in FDG uptake interpreted as epileptogenic region based on symmetry.</p> <p>When MRI normal or nonconcordant with video EEG or other imaging surgery was based on invasive EEG.</p> <p>Mean follow-up of 34 mo (range 12-67) after surgery.</p>	<p>81M, 36F.</p> <p>Mean age 28 years (range 12-46).</p> <p>32 patients met review inclusion criteria (normal MRI plus PET scan). Cannot determine numbers of TLE/ETLE pts, but ETLE \geq 50% of sample.</p>	MRI, SPECT.	<p>Pathologic findings.</p> <p>PET localisation considered correct when location of focal abnormality matched the operative site and location of histopathologic abnormality, or if somewhat diffuse PET abnormalities overlapped with operative site.</p>	<p>For pts with normal MRI plus PET scan, PET correctly localised the lesion in 19/32 pts (59.4%, 95% CI \pm 17.0%).</p> <p>For pts with normal MRI (n=36), 21 (58.3%) were seizure free, 1 (2.8%) had rare seizures, 8 (22.2%) had worthwhile improvement, and 6 (16.7%) had no worthwhile improvement post-surgery.</p>	<p>Outcome data includes 4 pts for whom PET was not conducted.</p> <p>PET did not contribute to surgical decision for pts with normal MRI.</p> <p>Patients may overlap with Kim, Wang et al 2000, and Won, Chang et al 1999.</p>

Study	Type of study	N	Patient source and selection	Study design	Patient characteristics	Comparator	Reference Standard	Results	Comment
(Tatidil et al 2000)	Localisation, correct localisation, and outcomes (level IV)	35	Pts who underwent anterior temporal lobectomy for medically intractable complex partial seizures. Not stated whether pts are consecutive.	Incremental value of FDG-PET. Unclear if prospective or retrospective. Presurgical evaluation consisted of interictal EEG, video EEG, MRI, PET and neurological examination. Depth EEG in 11 pts with no lateralisation from other modalities. PET images analysed semi-quantitatively by ROI asymmetry indices (AIs) in comparison with 100 normal controls. Surgery based on results from all available tests. Follow-up of 1-5 yrs after surgery.	17M, 18F. Mean age at surgery 33 years (range 18-52). 19 TLE patients met review inclusion criteria; normal MRI (n=14), or discordant MRI/EEG (n=5). For included pts: 9M, 10F. Mean age at surgery 36 years (range 18-52).	Video EEG, MRI, O15-PET.	Surgical outcome.	For pts with normal MRI or discordant MRI and EEG results (n=19), PET lateralised an abnormality in 13 pts (68.4%, 95% CI \pm 20.9%). Post-surgical outcomes: 8 (42.1%) seizure free; 9 (47.4%) significantly improved; and 2 (10.5%) not significantly improved. Correct localisation: 62.5% (95% CI \pm 21.8%) PET positive with good outcomes: 38.5% (95% CI \pm 21.9%)	-
(Won et al 1999)	Lateralisation and outcomes (level IV).	118	Consecutive pts who underwent surgery for medically intractable, epilepsy between October 1994 and September 1996.	Incremental value of FDG-PET. Retrospective. Presurgical evaluation consisted of video EEG, MRI and neuropsych studies in all pts. 95 pts had PET, 110 had interictal SPECT, 77 had ictal SPECT, and 45 with normal MRI or discordant imaging had intracranial EEG. PET scans underwent qualitative visual interpretation, with blinding to other tests. The area of greatest decrease in FDG uptake interpreted as epileptogenic region based on symmetry. When MRI normal or discordant with video EEG or other imaging, surgery was based on invasive EEG. Mean follow-up of 24 mo (range 12-35) after surgery.	74M, 44F. Mean age 27 years (range 8-55). 20 TLE and ETLE patients met review inclusion criteria (normal MRI plus PET scan).	MRI, SPECT.	Surgical outcome.	Lateralisation: 80.0% (95% CI \pm 17.5%) (correct in comparison with pathological diagnosis). Correct lateralisation: 84.6% (95% CI \pm 19.6%). For pts with normal MRI (n=26), 17 pts (65.5%, 95% CI \pm 18.3%) had good post-surgical outcome (Engels class I or II).	Outcome data includes 6 pts for whom PET was not conducted. PET did not contribute to surgical decision for pts with normal MRI. Patients may overlap with Hwang, Kim et al 2001, and Kim, Wang et al 2000.

Study	Type of study	N	Patient source and selection	Study design	Patient characteristics	Comparator	Reference Standard	Results	Comment
(Spanaki et al 1999)	Localisation.	53	Consecutive pts referred to Yale Epilepsy Program for presurgical evaluation for refractory localisation-related epilepsy. Inclusion criteria: diagnosis of medically intractable partial seizures; video EEG; ictal and interictal SPECT studies.	<p>Study designed to assess value of SPECT. FDG-PET included in presurgical evaluation.</p> <p>Unclear if prospective or retrospective.</p> <p>Presurgical evaluation consisted of video EEG, MRI, SPECT, history, neurologic and neuropsych studies in all pts. 45 pts had PET, and 27 with discordant imaging had intracranial EEG.</p>	<p>25M, 28F.</p> <p>Mean age 33.2 years (range 13-57).</p> <p>39 TLE and ETLE pts met review inclusion criteria. Considered eligible for data extraction if MRI was normal or discordant with scalp EEG, or if MRI showed hippocampal sclerosis, and a PET conducted. Discordance was defined as non-localising on EEG and localising on MRI, or if hemispheres or regions discordant (eg L on EEG and R on MRI; temporal on EEG and hippocampal on MRI; L on EEG and bilateral on MRI). Considered concordant if lateralised by EEG and localised in same hemisphere by MRI.</p> <p>For included pts: 16M, 23F.</p> <p>Mean age 32.6 years (range 13-56).</p>	PET, MRI, video EEG.	None for PET. Intracranial EEG or concordant non-invasive studies for SPECT.	29/39 pts (74.4%, 95% CI \pm 13.7%) with normal MRI or discordant MRI/EEG had a focal abnormality on PET (ie not normal or bilateral).	Study was designed to investigate the value of SPECT rather than PET.

Study	Type of study	N	Patient source and selection	Study design	Patient characteristics	Comparator	Reference Standard	Results	Comment
(Plotkin et al 2003)	Localisation.	38	<p>Pts with intractable partial epilepsy studied between 1998 and 2001.</p> <p>Not stated whether consecutive.</p> <p>16 pts (9M, 7F; age range 19-57) with no neurological or psychiatric history used as controls for SPM analysis.</p>	<p>Incremental value of visual, ROI, and SPM analysis of FDG-PET.</p> <p>Not stated whether prospective.</p> <p>Presurgical evaluation consisted of 5-day video EEG, MRI, and PET in all pts. Intracranial EEG conducted in 19 pts.</p> <p>PET interpreted without EEG results.</p> <p>Visual PET analysis by two independent experienced analysts. ROI interpreted by a single nuclear medicine physician (>10% to contralateral side considered a pathologic finding). Hypometabolic areas >100 voxels on SPM assumed to be significant.</p> <p>Min follow-up 24 months.</p>	<p>19M, 19F.</p> <p>Age range 11-59 yrs.</p> <p><u>Subgroup A:</u> 27 pts lateralised by scalp EEG. 20 of these pts with normal or bilateral MRI potentially eligible for review, but data was not disaggregated.</p> <p><u>Subgroup B:</u> 11 ETLE pts with bilateral EEG and normal on MRI eligible for data extraction.</p> <p>Surgery conducted on 6 pts in subgrp A.</p>	Presurgical evaluation.	Video-EEG, intracranial EEG, surgical outcomes.	<p>Localisation for subgroup B:</p> <p>PET (SPM $p < 0.005$) = 7/11 (63.6%, 95% CI \pm 28.4%)</p> <p>PET (SPM $p < 0.001$) = 1/11 (9.1%, 95% CI \pm 17.0%)</p> <p>PET (ROI) = 7/11 (63.6%, 95% CI \pm 28.4%)</p> <p>PET (visual) = 5/11 (36.4%, 95% CI \pm 28.4%)</p>	
(Juhasz et al 2003)	Localisation, accuracy, outcomes (Level IV).	27	<p>Pts with intractable epilepsy of neocortical origin.</p> <p>Not stated whether consecutive.</p> <p>A control group of 7 pts without epilepsy and normal MRI used for defining AMT-PET abnormalities. Mean age 9.7 yrs (range 8.2 – 14.3).</p>	<p>Incremental value of FDG PET.</p> <p>Unclear whether prospective or retrospective.</p> <p>Presurgical evaluation consisted of prolonged interictal and ictal scalp EEG monitoring, MRI, FDG PET and AMT PET. 15 pts also had subdural EEG.</p> <p>PET abnormalities identified by semiautomated software package.</p> <p>Intracranial EEG used to define resection for pts in which it was conducted. Pts with one-stage surgery underwent extensive intraoperative ECoG to define extent of resection.</p> <p>Mean follow-up of 19.8 mo (range 2-54).</p>	<p>17M, 10F.</p> <p>Mean age 6.2 yrs (\pm4.6; range 0.9 – 15.8).</p> <p>19 pts with normal MRI considered eligible for data extraction. 3 TLE, 16 ETLE.</p> <p>12 of these pts had surgery and available outcome data.</p>	Presurgical evaluation.	Surgical outcome.	<p>Localisation (all): 63.2% (95% CI \pm 28.5%).</p> <p>Localisation (TLE): 66.6% (95% CI \pm 53.4%).</p> <p>Localisation (ETLE): 62.5% (95% CI \pm 23.7%).</p> <p>Correct localisation (ETLE only): 75.0% (95% CI \pm 24.5%).</p> <p>PET positive with good outcomes (ETLE only): 85.7% (95% CI \pm 19.8%).</p> <p>Positive seizure control outcomes (all): 67.0% (95% CI \pm 26.6%).</p>	Localisation defined as "confined to one or two lobes".

Study	Type of study	N	Patient source and selection	Study design	Patient characteristics	Comparator	Reference Standard	Results	Comment
(Murphy et al 2004)	Lateralisation, outcomes (Level IV)	22	<p>Consecutive pts undergoing multimodality image-guided surgery (MMIGS) for medically refractory partial epilepsy at St. Vincent's hospital between April 1999 and October 2001.</p> <p>MMIGS defined as 2 or more imaging modalities in the intraoperative stereotactic guidance system used to identify surgical site.</p> <p>Drawn from 109 pts with epilepsy undergoing surgery during this time frame.</p>	<p>Incremental value of FDG PET. Retrospective.</p> <p>Included pts had a non-localising or non-lesional structural MRI (defined as no lesion, more than one lesion, lesion so large as to risk significant post-operative morbidity, or single lesion in eloquent cortex with risk of significant post-operative morbidity).</p> <p>In all pts, presurgical evaluation consisted of MRI (FLAIR and volumetric), functional MRI, scalp EEG, video EEG, ictal SPECT, PET, depth and subdural electrodes, neuropsych and psychiatric assessment. Wada performed where indicated.</p> <p>Localising imaging data coregistered for surgical planning.</p> <p>Mean follow-up of 26.4 mo (range 14-41).</p>	<p>12 M, 10F.</p> <p>Mean age 33 yrs (range 17-46).</p> <p>PET coregistered to MRI (9 pts) or PET/subdural electrode grids coregistered to MRI (1 pt). Therefore 10 eligible pts for inclusion in review.</p> <p>For included pts: 5M, 5F.</p> <p>9 TLE, 1 ETLE.</p> <p>Mean age 30.2 yrs (range 18-45).</p> <p>Mean follow-up 22.9 mo (range 14-39).</p>	Subdural electrode grids, SISCO, FLAIR MR.	Surgical outcome.	<p><u>Localisation:</u></p> <p>All: 100% (95% CI - 30.8%) TLE: 100% (95% CI - 33.6%) ETLE: 100% (95% CI - 97.5%)</p> <p><u>Correct localisation:</u></p> <p>All: 100% (95% CI - 30.8%) TLE: 100% (95% CI - 33.6%) ETLE: 100% (95% CI - 97.5%)</p> <p><u>PET+/good outcomes:</u></p> <p>All: 100% (95% CI - 30.8%) TLE: 100% (95% CI - 33.6%) ETLE: 100% (95% CI - 97.5%)</p> <p>9 pts had Engels class I outcome; 1 pts had Engels class II outcome.</p>	Unclear whether PET was non-localising in patients for whom other coregistered data was used to plan surgery.

Study	Type of study	N	Patient source and selection	Study design	Patient characteristics	Comparator	Reference Standard	Results	Comment
(O'Brien et al 2001)	Localisation, management change and outcomes (level IV)	55	<p>Consecutive pts referred for presurgical evaluation for medically refractory partial epilepsy at the Victorian Epilepsy Centres between November 1996 and April 1999.</p> <p>Visual presentation of PET images optimised by studying 10 pts with well localised temporal lobe epilepsy.</p>	<p>Incremental value of FDG PET in investigating outcomes and management change. Non-incremental contribution to localisation.</p> <p>Retrospective.</p> <p>Pts included if MRI and EEG provided insufficient information to proceed to surgery ("most" pts met this criterion, but it was not strictly enforced).</p> <p>Presurgical evaluation consisted of MRI, ictal video EEG, and PET.</p> <p>PET reviewed independently by 2 reviewers who were unaware of clinical, EEG and MRI findings.</p> <p>Final surgical localisation based on all available information.</p> <p>24 pts underwent surgery. Median post-surgical follow up was 17 mo (range 6-42).</p> <p>Management change assessed as follows: High: Unlocalised before PET and PET allowed further evaluation for surgery; Moderate: Localising info available but PET improved confidence and allowed for surgery; Low: PET confirmed seizure localisation by other non-invasive tests but did not change management; Contradictory: PET discordant with other localising info.</p>	<p>31M, 24F.</p> <p>Mean age 34 yrs (range 16-63).</p> <p>41 TLE, 14 ETLE.</p>	MRI, video EEG.		<p><u>Localisation (all pts):</u></p> <p>All: 42/55 pts (76%, 95% CI \pm 11.3%)</p> <p>TLE: 37/41 pts (90%, 95% CI \pm 9.1%)</p> <p>ETLE: 4/14 pts (36%, 95% CI \pm 25.1%)</p> <p>PET localisation in TLE pts significantly greater than ETLE pts (p=0.0001).</p> <p><u>Outcomes:</u></p> <p>18/21 pts (86%) with localising PET had class I outcome; 2/21 pts (10%) had class II; 1/21 (5%) had class III.</p> <p>1/3 pts (33%) with nonlocalising PET had class I; 1/3 pts (33%) had class II; 1/3 (33%) pts had class IV.</p> <p><u>Change in management:</u></p> <p>Impact of PET was high in 25/55 pts (45%), moderate in 7/55 pts (13%), and low in 23/55 (42%).</p>	<p>Selection criteria not strictly enforced, so an indeterminate number of pts are included who may have been localised by MRI/EEG.</p> <p>Multivariate analysis presented but not considered here.</p>

Study	Type of study	N	Patient source and selection	Study design	Patient characteristics	Comparator	Reference Standard	Results	Comment
(Meyer et al 2001)	Lateralisation.	43	Consecutive pts evaluated for surgery for drug-refractory complex partial seizures at the Seizure Centre of the Department of Neurology of the Hospital of the University of Pennsylvania between January 1998 and December 1999.	<p>Incremental value of FDG-PET. Retrospective.</p> <p>Pts included if had drug refractory complex partial seizures with PET, MRI and MRS within a maximum of six weeks.</p> <p>Presurgical evaluation consisted of neurological and neuropsych exam, video EEG, intracranial EEG, PET, MRI and MRS.</p> <p>PET images interpreted visually by at least two experienced nuclear medicine physicians, and interpretations made by consensus. Not stated whether other clinical/imaging information available.</p> <p>Considered lateralised if marked one-sided hypometabolism; possibly lateralised if findings mild or bilateral hypometabolism with one side more pronounced; and not lateralised if no abnormality or equally bilateral.</p> <p>Surgery based on surface and intracranial EEG, clinical exam and imaging data.</p> <p>Mean post-surgical follow-up was 20.1 mo (± 7.7; range 7.6 – 35.7).</p>	<p>18M, 25F.</p> <p>Mean age at PET study 34.6 yrs (± 11.6; range 15.7 – 61.8).</p> <p>20 pts with "unremarkable" MRI and/or not lateralised on EEG with a valid PET scan considered eligible for data extraction.</p> <p>15 TLE, 5 ETLE.</p> <p>15 pts proceeded to surgery.</p>	MRI, EEG, MRS.	-	<p>PET lateralised 10/20 pts (50%), possibly lateralised 4/20 pts (20%) (total 70%, 95% CI $\pm 20.1\%$)</p> <p>TLE: lateralised or possibly lateralised 93.3% (95% CI $\pm 12.6\%$).</p> <p>ETLE: lateralised or possibly lateralised 0.0% (95% CI + 52.2%)</p>	Unable to report on surgical outcomes.

Study	Type of study	N	Patient source and selection	Study design	Patient characteristics	Comparator	Reference Standard	Results	Comment
(Salanova et al 2001)	Localisation, outcomes (Level IV).	77	<p>Pts with medically refractory TLE evaluated after 1990. 51 pts had surgical resection after video EEG and follow-up of at least 2 years (group 1). 26 pts had non-concordant non-invasive tests and were studied with invasive EEG (group 2).</p> <p>Unclear if consecutive.</p>	<p>Incremental value of FDG PET. Unclear if prospective or retrospective.</p> <p>Presurgical evaluation consisted of neurologic exam, psychometric testing, MRI, video EEG, interictal and ictal SPECT, PET and IAP.</p> <p>PET analysed visually by experienced nuclear medicine physicians blinded to EEG, and by two neurologists. Pts from group 2 had intracranial EEG.</p> <p>Unclear how the decision to proceed to surgery was made. Implied that this was the concordance of non-invasive tests in group 1, and invasive EEG results in group 2.</p> <p>Postsurgical follow-up was at least 2 yrs (Group 1 range 2-7; group 2 range 2-8).</p>	<p>Pts from group 2 relevant to review (n=26).</p> <p>Mean age at surgery 39.7 yrs (range: 14-48).</p> <p>Gender breakdown not reported.</p> <p>18 TLE pts with insufficient non-invasive information to proceed to surgery who had a PET scan eligible for data extraction.</p>	Presurgical evaluation.	-	<p>PET showed temporal lobe hypometabolism in 7/18 pts (38.8%, 95% CI ± 22.5%).</p> <p>6 pts proceeded to surgery, 4 (67%) became seizure-free, 1 (17%) had worthwhile improvement, and 1 (17%) had no improvement.</p>	<p>PET included in presurgical workup, so PET's inability to localise is part of criterion of "insufficient non-invasive information to proceed to surgery". Therefore different pt group to just MRI negative or MRI/EEG discordant.</p> <p>Information such as gender, surgical decision criterion and post-surgical follow-up not stated.</p>

Study	Type of study	N	Patient source and selection	Study design	Patient characteristics	Comparator	Reference Standard	Results	Comment
(Juhasz et al 2000)	Outcomes.	12	Pts undergoing resective surgery for treatment of medically intractable neocortical epilepsy. Unclear if consecutive.	Incremental value of PET coregistered to MRI. Unclear if prospective or retrospective. Pts included if met the following criteria: 1) medically intractable epilepsy of neocortical origin based on seizure semiology and ictal EEG; 2) focal cortical areas of decreased FDG metabolism on PET not associated with structural abnormalities on MRI. All pts with temporal EEG foci were normal on MRI (ie nonconcordant). Presurgical evaluation included ictal EEG, MRI, PET, and intracranial EEG. PET/MRI analysed by objective method of defining cortical asymmetries. Mean postsurgical follow-up was 15.3 mo (\pm 5.3).	7M, 5F. Mean age 10.8 yrs (range 2-19).	Presurgical evaluation.		Outcomes were Engels class I (seizure-free) for 8 pts (66.7%), 1 was class II (8.3%), 2 were class III (16.7%), and 1 pt was class IV (8.3%).	Localisation value of FDG PET could not be extracted.

Appendix E Excluded Studies

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Abbreviations

AED – Antiepileptic Drug

AIHW – Australian Institute of Health and Welfare

CT – Computed Tomography

DALYs – Disability Adjusted Life Years

DARE – Database of Abstracts of Reviews of Effectiveness

DBS – Deep Brain Stimulation

EEG – Electroencephalogram

FDG – 2-[¹⁸F]fluoro-2-deoxy-D-glucose

HTA – Health Technology Assessment

IAP – Intracarotid Amobarbital Procedure

ILAE – International League Against Epilepsy

keV - kilo-electron-Volts

MBS – Medicare Benefits Scheme

MRI – Magnetic Resonance Imaging

MSAC – Medical Services Advisory Committee

NHMRC – National Health and Medical Research Council

PBS – Pharmaceutical Benefits Scheme

PET – Positron Emission Tomography

ROI – Region of Interest

SPE(C)T – Single Photon Emission (Computed) Tomography

SPM – Statistical Parametric Mapping

WHO – World Health Organisation

VNS – Vagal Nerve Stimulator

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