Positron Emission Tomography: Clinical Status in the United States in 1987

*ACNP/SNM Task Force on Clinical PET**

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Positron emission tomography (PET) is a method for quantitative imaging of regional function and chemical reactions within various organs of the living human body. PET therefore has the potential for providing unique, clinically important information about disease processes. To date, most PET studies have been directed towards elucidation of normal and pathologic physiology and have been performed in research environments. However, with increasing experience, it has become apparent that the type of information obtainable from PET studies is clearly useful as well for routine diagnosis, prognostication, and treatment planning as part of the clinical evaluation of individual patients. Since these clinical applications of PET are becoming more evident in the literature, the Society of Nuclear Medicine and the American College of Nuclear Physicians appointed a task force to review the clinical utility of PET and to develop a document for submission to the Health Care Financing Administration. The full document reviews the principles of PET and those clinical applications the task force considered appropriate for reimbursement. This paper briefly presents the clinical applications of PET for which effectiveness is well documented and there is a general consensus regarding clinical utility.

RELATION TO OTHER IMAGING MODALITIES

PET is an imaging modality that provides regional as well as global information about physiology or chemistry within various body organs with sensitivity and specificity comparable to that obtained by radioimmunoassay in studies of body fluids. Other imaging modalities, such as x-ray computed tomography (CT) and magnetic resonance imaging (MRI), provide predominantly anatomic information. CT scanning is based on the portrayal of the distribution of attenuation of x-rays passing through the body. The attenuation may be either intrinsic to the tissue or produced by the administration of radio-opaque contrast material. MRI exploits the variation in regional concentrations of hydrogen and nuclear relaxation parameters to generate image contrast and to provide information about free water content, relative blood flow and the concentration of contrast agents (*1*).

In most diseases, chemical changes occur prior to anatomic changes. PET can detect functional abnormalities before anatomic changes have occurred, as for example, in epilepsy (*2*), Huntington's disease (*3*), cerebrovascular disease (*4*) or coronary artery disease (*5*). Abnormalities detected by PET imaging can be related to microscopic findings, e.g., neuronal loss and gliosis in Alzheimer's disease (*6*), whereas gross anatomic changes are generally evident by the time disease is detectable by CT or MRI.

COST CONSIDERATIONS

The costs of equipment for doing PET studies have limited the number of institutions that have acquired the requisite instrumentation. Most PET systems are now produced individually, and the cost advantages of mass production have not yet been realized in this market. Cost reductions also could occur in the change to the simplified and constrained technology of a clinical environment compared to the flexibility required in a research setting. PET scanners are priced in the $1.0 to $1.8 million range for high-resolution systems (*7–10*). Cyclotrons for radiopharmaceutical production in the hospital environment also cost in the range of $1.0 to $2.0 million. The sharing by several institutions of radiopharmaceuticals produced in a regional cyclotron and use of generator- derived radiopharmaceuticals are both possible means to reduce the costs of PET studies. The cost of facility renovations for a PET scanner and cyclotron can range from $50,000 to more than $1.0 million. Operating costs are estimated to be $400,000 to $1.0 million per year depending on the

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laboratory. The number of procedures per day in a typical clinical facility will be 6–12 (*8–10*). Technical charges are estimated to be $600 to $1500 per patient depending on the complexity of the study, workload, whether a cyclotron is used, etc. Thus, these charges are not significantly different from charges for other imaging studies involving advanced technology.

CORONARY ARTERY DISEASE

Coronary artery disease continues to be the leading cause of death in most technologically advanced countries despite a declining mortality from heart disease since 1968. Heart disease is responsible for 640,000 deaths each year in the United States, and accounts for almost a third of all deaths between the ages of 35 and 64 years. Up to 13% of middle-aged men in the general population have coronary artery disease (*11–12*), most without symptoms. The first sign of heart disease in many persons is sudden death or acute myocardial infarction. Approximately 60% of patients who have coronary artery disease die suddenly or have a myocardial infarction without prior symptoms (*13–15*). Silent myocardial ischemia is being recognized with increasing frequency and may indicate a less favorable prognosis than its symptomatic counterpart (*16*). Control of risk factors is helpful, but is limited by the low sensitivity and specificity of risk factor analysis for identifying individuals with coronary heart disease. Two thirds of healthy adult males, aged 40–55 yr, with high serum cholesterol and hypertension remain well during the 25 yr subsequent to the discovery of these risk factors.

Current noninvasive diagnostic techniques are helpful, but not perfect. The sensitivity and specificity of exercise thallium-201 (^{201}Tl) imaging for detecting coronary artery disease were initially reported to be ~80–90% but more recent studies have demonstrated a lower specificity. A multicenter study of 1,096 patients who underwent intravenous dipyridamole-^{201}Tl studies and coronary arteriography had a sensitivity of 85% and a specificity of 52% (Rohanski A: Boehringer Ingelheim Pharmaceuticals, Inc., Registry, personal communication). Exercise-redistribution studies also were performed in 146 of the patients, and the sensitivity and specificity were 86% and 50%, respectively. Rest-exercise ventricular function studies have a sensitivity and specificity similar to that of the multicenter study of ^{201}Tl imaging (*17*). PET scanning can accurately identify patients with coronary artery disease (*18–21*). Furthermore, in those patients with diagnosed coronary artery disease, PET studies can determine the physiologic severity of stenosis noninvasively and thus avoid unnecessary diagnostic catherization or other procedures (*21*). PET can accurately determine myocardial viability which is a important factor in properly selecting the appropriate patients for revascularization procedures (*22–24*).

Positron imaging studies of the heart consist of myocardial perfusion studies performed with either generator-produced rubidium-82 (^{82}Rb) or cyclotron-produced nitrogen-13 (^{13}N) ammonia and myocardial viability studies performed with fluorine-18 fluorodeoxyglucose (FDG). Several studies have documented the accuracy of myocardial perfusion imaging with PET in the diagnosis of coronary artery disease (*18–20,24–32*). The PET studies for detecting coronary artery disease have been rest-stress perfusion studies. The stress may be supine bicycle exercise (*20*), which is presently used clinically for rest-exercise ventricular function studies, or pharmacologically induced with intravenous dipyridamole (*33*), which is presently used clinically in conjunction with ^{201}Tl scintigraphy.

The sensitivity of PET for diagnosing coronary artery disease, by comparison with coronary arteriography, is >95% and the specificity is similarly high, even in asymptomatic individuals (Table 1). More than 350 patients with suspected coronary artery disease have had PET studies and coronary arteriography (*19,20,25, 34*). The studies have uniformly demonstrated very high sensitivity and specificity. PET perfusion studies appear to be more accurate than the noninvasive studies presently being used in the evaluation of patients with suspected coronary artery disease, and reliably assess which arteries are involved (*34*) and the severity of narrowing (*21*, Demer et al: personal communication).

Since PET perfusion imaging is more accurate than ^{201}Tl scintigraphy for diagnosing and assessing severity of coronary artery disease, PET likely will replace the thallium study in those centers where it is available. Fewer coronary arteriograms would be performed following the PET study than ^{201}Tl study since there would be less diagnostic uncertainty after the PET study. PET

TABLE 1
PET Detection of CAD: Correlation with Coronary Arteriography

Study (references)	No.	Radiopharmaceutical	Sensitivity (%)	Specificity
Schelbert et al. (*19*)	32	$^{13}NH_3$	97	100
Tamaki et al. (*20*)	32	$^{13}NH_3$	95	100
Gould et al. (*25*) (included in Demer et al.)	50	Rb-82, $^{13}NH_3$	95	100
Grover McKay et al. personal communication	25	Rb-82	96	
Demer et al. personal communication	193	Rb-82, $^{13}NH_3$	94	95
Yonekura et al. (*34*)	49	$^{13}NH_3$	97	100

perfusion studies can be used for noninvasive follow-up of patients who have undergone percutaneous transluminal coronary angioplasty, and can reduce the numbers of repeat angiograms which are now frequently performed to identify the 20–25% of patients who develop restenosis (*30*).

Myocardial viability can be determined at rest by sequential imaging with a perfusion tracer and FDG (*22–24,35–42*) (Table 2). Myocardial perfusion imaging indicates areas with decreased perfusion that could represent either ischemic but viable myocardium or infarcted myocardium. FDG accumulation increases in ischemic myocardium compared with normally perfused myocardium. Necrotic myocardium does not accumulate FDG (*22,23,35*). In normal myocardium in the fasting state, fatty acids are the primary substrate for producing high-energy phosphate. The fatty acid metabolic pathway is sensitive to ischemia, and the myocardium compensates by increasing glucose utilization through increased extraction of glucose and increased breakdown of glycogen. Thus, increased FDG accumulation occurs in ischemic myocardium.

Patients with coronary artery disease and decreased left ventricular function from one or more dysfunctional wall segments have been evaluated with [^{13}N] ammonia and FDG prior to coronary artery bypass grafting (*22*). Viable myocardium was determined by the finding of normal flow and FDG accumulation or the finding of decreased flow and increased FDG accumulation in dysfunctional segments. Myocardial scar was determined by the finding of decreased flow and decreased FDG accumulation. Regional wall motion was evaluated pre- and postoperatively. Regional function improved after bypass grafting in 85% of the segments identified as viable on the PET study, whereas 96% of segments identified as scar did not show improved regional wall motion. Of the 15% of viable segments that did not show functional improvement, the majority were septal segments which are known to be impaired by surgery. When PET identified three or more myocardial regions as viable, a significant improvement in left ventricular ejection fraction was noted after surgery.

TABLE 2
PET Assessment of Myocardial Viability

Study (reference)	#	Patient group
Marshall et al. (*23*)	15	Myocardial ischemia/ infarct
Tillisch et al. (*22*)	17	Coronary artery bypass graft surgery
Brunken et al. (*35*)	20	EKG Q wave infarction
Brunken et al. (*36*)	12	Persistent planar ^{201}Tl perfusion defects
Tamaki, et al. (*37*)	20	Thallium-201 perfusion imaging
Brunken et al. (*38*)	26	Persistent SPECT ^{201}Tl perfusion defects
Camici et al. (*24*)	22	Exercise induced ischemia
Schwaiger et al. (*39*)	15	Acute myocardial infarction
De Landsheere et al. (*40*)	24	Acute myocardial infarction and thrombolysis
Araujo et al. (*41*)	11	Unstable angina

In another study of patients with previous infarction, PET studies identified viable myocardium in many segments that had fixed defects on ^{201}Tl imaging and thus by conventional criteria would be considered nonviable (*36*). In patients with acute infarction, areas showing matched decreases in both flow and FDG accumulation did not recover contractile function. In approximately 50% of segments with normal or increased FDG accumulation but decreased flow, regional function was improved 6 wk later. Approximately 200 patients have had PET myocardial viability studies (Table 2). These studies document the ability to identify viable myocardium with PET and its use in selecting patients with ventricular dysfunction most likely to be improved by revascularization procedures.

More than 100,000 patients have coronary artery bypass surgery annually in the United States at a cost of more than 7 billion dollars. Surgical intervention is more likely to be successful in a patient with a low ejection fraction if the PET study shows that one or more dysfunctional segments are viable. Identification of even a small percentage of patients not expected to benefit from coronary artery bypass graft surgery would result in large savings in health care expenditures.

Epilepsy

Epilepsy is one of the most common diseases of the nervous system. Approximately 800,000 Americans have partial seizures that do not generalize to major motor or complex partial seizures. For most patients with partial epilepsy, diagnosis and classification leading to selection of medical therapy are based on the use of surface electroencephalography (EEG), which records electrical activity associated with neuronal activity. However, for the subset of patients (~20%) whose seizures are inadequately controlled by medication, additional information about localization of the epileptic focus is required if surgical therapy is anticipated. Radiological techniques, such as CT scanning and MRI, show no structural abnormalities in the majority of these patients. Special localizing measures, including intraoperative electrocorticography and direct recordings from stereotaxically-implanted depth electrodes, have been found valuable for improved localization, but these techniques can give rise to conflicting results and are themselves accompanied by the risks of a surgical procedure. In such a setting, PET can provide

independent confirmatory information regarding the presence and site of a discrete epileptogenic lesion.

During focal seizures, brain metabolism and blood flow are increased at the site of onset of the seizures and in regions to which the seizure activity is propagated. Between seizures (interictal state), both metabolism and blood flow are reduced at the site of onset. When PET was first applied in epilepsy (*43*), it was anticipated, and subsequently confirmed, that PET imaging would localize these focal changes in cerebral metabolism and perfusion and thus provide unique diagnostic information, which would be useful in the management of patients with epilepsy.

PET techniques most useful in the study of epilepsy include determinations of glucose utilization (FDG), oxygen utilization (^{15}O oxygen) and cerebral perfusion [^{13}N]ammonia and ^{15}O water).

PET scans obtained during partial seizures have shown marked increases in local brain metabolism and perfusion at the site of seizure onset, but because of propagated neuronal activity, the ictal scans are less useful in predicting the locus of epileptic activity than those made during the interictal state (*43–46*). PET scans made during nonfocal seizures show a generalized increase in brain metabolism and perfusion (*43,45,47, 48*). Unlike the typical PET scans found in partial epilepsy, no focal changes are found during interictal or ictal scans of patients with petit mal seizures. A diffuse increase of metabolism is seen at the time of the petit mal seizure.

PET scans obtained during the interictal state are most valuable in the management of the patient with partial epilepsy. The results of interictal PET scans in patients with partial epilepsy have been compared with the results of CT and EEG in multiple reports (*43,48–72*). The results have been essentially the same in the 50-patient series reported from UCLA (*43,55*), the 20-patient series from NIH (*69*), and the 24-patient series from Montreal (*66*). PET results have been compared with interictal EEG findings, frequently paired with depth electrode measurements, and pathologic evaluations from resected specimens. Approximately 70% of these patients demonstrate zones of hypometabolism on interictal FDG scans. PET and EEG are complementary methods with the EEG providing identification of seizure phenomenon with limitations in spatial localization and PET providing accurate localization. Focal abnormalities may be identified with PET even if EEG data are unable to identify a unique focus. The combined use of surface EEG and PET has eliminated the need for depth electrodes in ~50% of surgical candidates. PET can aid in the localization of the site when the EEG findings are indeterminate. EEG can verify the epileptogenic nature of a zone of hypometabolism determined by PET. Furthermore, an excellent correlation has been obtained between the site of hypometabolism as determined by PET and the presence of a pathologic abnormality in the surgical specimen.

A good correlation exists between metabolic and combined electrophysiologic techniques with respect to localization of the epileptogenic focus. Either technique alone can give false-positive or false-negative results, but when used in combination they yield more reliable localizing information. The EEG is necessary for confirming that a hypometabolic zone is epileptogenic. The PET scan helps determine whether an abnormal EEG focus is likely to represent a primary epileptogenic region or propagation from a distance and provides an independent, spatially accurate confirmation of the epileptogenic site.

Brain Tumors

Tumors involving the central nervous system are estimated to comprise 2–5% of all tumors (*73*) and according to the results of the Third National Cancer Survey (1973–1974) account for at least 3.9–4.4 deaths/100,000 population per annum in the United States (*74*). This incidence rate would predict approximately 11,000–15,000 new primary brain tumor cases per year in the 1980's in the United States making malignant brain tumors more common than Hodgkin's Disease (*75*). Of CNS tumors, those classified as glioblastoma multiforme represent between 15–20% of all intracranial neoplasms and account for 31–64% of all primary gliomas (*76*); based on incidence figures, the number of deaths attributable to glioblastoma multiforme alone would be 2,500–5,000 per year (*77*).

Progress in the treatment of malignant gliomas is at a virtual standstill. The most recent multi-center trials of therapy of glioblastoma multiforme, which used surgery, radiotherapy and BCNU, have shown that combined surgery and radiotherapy increased median survival from 17–37.5 wk but that adding BCNU increased survival only an additional two weeks (*77,78*). Efficacy of surgical resection and external radiotherapy have reached a zenith, principally because of intolerable side effects, especially radiation necrosis of the brain. Radiation necrosis was found in five of 17 autopsy cases among patients in the National Cooperative Brain Tumor Group series who had received 5,000–6,000 rad of external radiation therapy to the brain and neuraxis. The true incidence of radiation necrosis of the brain following such radiation might be much higher if these patients survived longer. As neurologic symptoms recur or change in patients treated with radiation, it is virtually impossible to distinguish radiation necrosis and gliosis from tumor recurrence by conventional imaging techniques or clinical examination. A second craniotomy and tissue biopsy must often be performed.

PET studies in patients with gliomas have provided important clinical information (*79,80*). Di Chiro (*80*) has found the PET-FDG method "extremely useful in

patient management" in more than 350 patients with brain tumors. There is an excellent correspondence between the increasing concentration of FDG by a tumor and the increasing malignancy of the tumor (histologic grade) (*80,87*). In a report of 100 patients with primary tumors, DiChiro (*80*) noted increased FDG accumulation subjectively in all 60 high-grade (grade III and IV) lesions and in only four of 40 low-grade lesions. The calculated glucose metabolic rates showed greater overlap between the high-grade and low-grade lesions. The greater overlap in the metabolic rates was related to several factors including prior radiation therapy and partial volume averaging in small tumors. Even with these limitations, a significant difference in values was found between the low-grade and high-grade lesions. Tyler et al. (*82*) recently reported on 16 patients with suspected high-grade gliomas who were untreated. Only two of the patients had low-grade tumors (grade II), and the glucose metabolic rate was not significantly different from the 14 patients with grade III and IV tumors. The study of Tyler et al. differs from that of Di Chiro since they selected patients with suspected high-grade tumors, excluded patients with previous treatment, and did not perform subjective image analysis.

A marked worsening of prognosis is found as the FDG uptake increases (*80,83*). Forty-five patients with high-grade tumors who had surgery and radiation therapy were studied. Thirty-two of these patients also had chemotherapy. The glucose metabolic rate of the tumor was compared to the opposite normal parenchyma, and this metabolic ratio had a highly significant correlation with length of survival. The median metabolic ratio for the 45 patients was 1.4. Patients with ratios <1.4 had a median survival of 19 mo. Patients with ratios >1.4 had a median survival of 5 mo. Furthermore, an elevated metabolic ratio better predicted poor prognosis than did histologic classification of the tumor as grade III or grade IV.

Studies of glucose metabolism using FDG and studies of blood flow, blood volume and oxygen metabolism using ^{15}O were conducted sequentially on the same set of eighteen patients to further characterize the malignancy of gliomas (seven low grade, eleven high grade gliomas) (*84*). The results confirmed previous findings (*85*). Cerebral blood flow and blood volume were variable and seemingly unrelated to tumor grade. Oxygen metabolism and oxygen extraction were reduced significantly relative to values in contralateral tissue. Glucose metabolism was demonstrated to increase with tumor grade. Cerebral blood flow, oxygen metabolism, and glucose metabolism were reduced in contralateral grey matter relative to normal volunteers.

The FDG uptake in a tissue region, after therapy for brain tumor, can be used to discriminate between the recurrence of brain tumor and damage to normal brain tissue, particularly radiation necrosis or edema (*86–88*). Radiation therapy is considered the treatment of choice as an adjunct to decompressive surgery in patients with glioblastoma multiforme but this therapy is seldom, if ever, curative, and it is often difficult to distinguish between recurrent tumor and radiation necrosis after therapy. While CT is unable to differentiate between new tumor growth and postoperative development of necrotic tissue, the distinction is relatively easy with PET scanning, because the necrotic brain does not metabolize glucose. Recurrent tumor exhibits highly active glucose metabolism and irradiated, non-necrotic brain has active, although subnormal glucose metabolism. Patronas et al. (*86*) reported that the FDG study accurately predicted the biopsy or autopsy results in five patients who had similar clinical and CT findings. Two patients had radiation necrosis and three patients had recurrent tumors. Doyle et al. (*87*) studied nine patients to differentiate tumor recurrence from radiation necrosis. A ^{82}Rb study was performed to identify abnormalities in the blood-brain barrier in addition to the FDG study. The ^{82}Rb study was unable to differentiate recurrent tumor from necrosis. The FDG study was accurate in identifying recurrent tumor in four patients who were biopsied and in identifying radiation necrosis in five patients, three of whom were biopsied. Di Chiro et al. (*88*) have recently reported their results in 95 patients with primary and metastatic brain tumors. Radiation necrosis was diagnosed in ten patients and tumor was diagnosed in 85 patients. The PET-FDG result was verified in every patient by surgery and/or autopsy. In addition, four patients with cerebral necrosis from chemotherapy were correctly characterized by the FDG study. MRI and CT were not able to differentiate tumor from radiation or chemotherapy necrosis.

Thus, PET studies can provide unique clinical information for management of patients with gliomas. Diagnostic and prognostic information is provided by the PET studies at the time of presentation. Furthermore, recurrence of tumor after therapy is accurately determined by PET whereas other imaging modalities are less accurate in this determination.

SUMMARY

PET studies are now being used to provide unique clinical information in several conditions. PET is an accurate, noninvasive method of identifying patients with coronary artery disease. Furthermore, PET studies can accurately differentiate patients who will or will not benefit from revascularization procedures. In patients with partial epilepsy being considered for surgery, PET studies provide spatial localization of the focus that complements other tests in improving the surgical management of these patients. PET studies give important diagnostic and prognostic information in the management of patients with gliomas and can direct recurrence of tumor and distinguish it from radiation necrosis.

These uses of PET are well documented, and their utility has been independently confirmed in several institutions. Several other areas of research are being pursued with PET, and these will probably develop into clinically useful procedures in the future.

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