Clinical PET: A Technology on the Brink

R. Edward Coleman

Department of Radiology, Duke University Medicine Center, Durham, North Carolina

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The study of body chemistry has always been an important aspect of the discipline of nuclear medicine. Positron emission tomography (PET) is an elegant technique for characterizing multiple aspects of body chemistry. This promising technology is on the brink of limited utilization in the routine practice of nuclear medicine. The reasons that PET is not being utilized in more centers are complex. A review of the development of PET technology, the radiopharmaceutical approval process, reimbursement policies and the current utilization of the instrumentation will help in understanding the reasons that clinical PET is on the brink.

PET was developed in the early 1970s and its research applications were obvious and were pursued. PET was utilized in the research environment in a small number of major academic medical centers for many years, and the clinical applications of PET have now been demonstrated (Table 1). In the mid to late 1980s the information available from the PET studies was shown to be important for selected neurologic and cardiologic indications (*1–4*). Neurologic indications include evaluation of patients with complex partial seizure disorder for whom treatment by surgery is being considered, determination of the degree of malignancy of brain tumors, differentiation of recurrent brain tumor from necrosis after therapy and dementia. The cardiologic indications include the detection of coronary artery disease and the determination of myocardial viability. However, these clinical uses of PET are the subject of controversy (*4,5*). The oncologic applications (*6–13*) may be the major utilization of PET in the future. PET is very accurate in the determination of malignancy in patients presenting with solitary pulmonary masses (*6,8,9*) and in determining the grade of malignancy of a tumor (*10,11*). PET provides unique metabolic information in the differentiation of tumor from scar after therapy (*7*).

PET requires expensive technology for the performance of the studies. Many centers now performing clinical PET studies have a tomograph and cyclotron because these centers are performing both research and clinical studies. The costs of purchasing, maintaining and operating a cyclotron are excessive for most centers that want to perform only clinical studies. Thus, a center may purchase a tomograph and use it with generator-produced ^{82}Rb and/or ^{18}F-2-fluorodeoxyglucose (FDG) provided by a regional radiopharmacy. The studies of current clinical interest can be performed using ^{82}Rb and FDG. For clinical PET to be widely utilized, regional distribution of FDG will be extremely important. Fluorine-18-fluoride was distributed nationally as a bone scanning radiopharmaceutical in the early 1970s and FDG could be similarly distributed.

TABLE 1
Clinical Indications for PET

Neurologic
Complex partial seizure disorder being considered for surgical treatment.
Dementia
Brain tumors
Determination of degree of malignancy.
Differentiation of recurrent tumor from necrosis after therapy.
Cardiologic
Detection of coronary artery disease.
Determination of myocardial viability.
Oncologic
Evaluation of solitary pulmonary masses.
Grading degree of malignancy of a tumor.
Differentiation of tumor from scar after therapy.

PET is not widely used clinically for several reasons, but the major limitation is the absence of policies of reimbursement for clinical PET studies by third-party payers (*14,15*). Blue Cross/Blue Shield has a national policy for paying for PET scans for two indications: complex partial seizure disorder being considered for surgery and the differentiation of recurrent primary brain tumor from necrosis. All other conventional diagnostic techniques including SPECT should be performed with inconclusive results before the PET study is performed. Some other insurance companies have policies for reimbursement for PET scans but most do not.

A major third-party payer is the Health Care Financing Administration (HCFA) which administers Medicare. The HCFA has referred the review of PET to the Office of Health Technology Assessment (OHTA). OHTA has reviewed PET, but the HCFA has determined that the result of the review will not be released until FDG has received a

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For correspondence or reprints contact: R. Edward Coleman, MD, Box 3949, Dept. of Radiology, Duke University Medical Center, Durham, NC 27710.

new drug application (NDA) from the Food and Drug Administration (FDA). Rubidium-82, one of the radiopharmaceuticals necessary for performing the studies under review, has received an NDA. FDG has not yet received an NDA. Attempts have been made to obtain the results of the OHTA review for the indications using ^{82}Rb, but OHTA will not release a part of the review.

The HCFA has determined that the FDA will be its consultant to determine the safety and effectiveness of radiopharmaceuticals. If the FDA declares that it has jurisdiction over a radiopharmaceutical used in a procedure to be reimbursed by the HCFA, then an NDA is needed to demonstrate the safety and effectiveness of the radiopharmaceutical. If the FDA would determine that it does not have jurisdiction over the radiopharmaceutical, then the HCFA would have the radiopharmaceutical evaluated by some other mechanism which has not been defined.

In 1988, the FDA described its proposed mechanism for regulating PET radiopharmaceuticals, including the use of the NDA process. Representatives of the FDA noted that PET radiopharmaceuticals such as FDG have a long history of safety, and that the NDA process could be facilitated for these radiopharmaceuticals. Even though members of the PET community expressed concern about current good manufacturing practice (cGMP) standards required by an NDA, representatives of the FDA stated that the production standards could easily be met by a PET facility and would not be much different than required by state boards of pharmacy.

The Institute for Clinical PET (ICP) worked with the FDA to develop a mechanism for obtaining an NDA. The mechanism included the ICP's preparation of both clinical and chemistry drug master files (DMFs) which could be referred to by a laboratory submitting an NDA. The site-specific information would be in the NDA, but all the general information would be included in the DMFs. Representatives of ICP were assured by representatives of the FDA that PET laboratories would be able to meet the cGMP standards that would be written for PET facilities. The DMFs were prepared and submitted by the ICP and an NDA was submitted. The clinical DMF was recommended for acceptance by the Medical Imaging Drugs Advisory Committee in May 1992. The chemistry and manufacturing DMF is presently under review.

The initial site submitting an NDA has had cGMP site visits, and the laboratory has not met the requirements at this time. Although some minor changes have been made in the guidelines for a cGMP inspection of a PET facility, it is unlikely that a PET facility can meet the cGMP standards, which were written for drug manufacturers who produce large quantities of therapeutic drugs. The cGMP standards are voluminous, and a few of the multitude of requirements include environmental facility controls (a "clean" room or "clean" area), control of raw materials and components, process validation and extensive documentation. Most PET laboratories would need additional manpower, space and equipment to meet these standards. The process of attempting to obtain an NDA through the FDA-proposed mechanism has been unsuccessful. Even if the first center does obtain an NDA, the process is inappropriate for most PET centers because they could not meet the cGMP requirements.

A public hearing was held at the FDA on March 5, 1993 to discuss regulation of PET radiopharmaceuticals. The FDA confirmed its intent to regulate PET radiopharmaceuticals by the NDA route. It also noted its plan to regulate cyclotrons and automated synthesis devices through the 510(k) process. The organizations representing the PET community (Society of Nuclear Medicine, American College of Nuclear Physicians, American College of Radiology, Institute for Clinical PET and American Pharmaceutical Association), representatives of the PET industry and interested individuals were uniform in their criticism of the planned approach to regulate PET radiopharmaceuticals. Several organizations suggested the development of an expert panel consisting of representatives from the FDA and the PET community to recommend to the FDA an appropriate approach for regulating PET radiopharmaceuticals. A specific suggestion for regulating clinical PET radiopharmaceuticals was to develop the equivalent of the Radioactive Drug Research Committee (RDRC), which has oversight of research radiopharmaceuticals. The RDRC reports to the FDA, and thus the FDA would maintain its oversight of PET radiopharmaceuticals with a committee devoted to clinical PET radiopharmaceuticals. The outcome of the March 5 meeting will not be known for several months.

The major reason for obtaining an NDA for FDG is to have an NDA-approved radiopharmaceutical. The NDA will result in the release of the OHTA review and in the determination of the reimbursement policy by the HCFA. The policy developed by the HCFA greatly influences other third-party payers. Furthermore, several third-party payers will not develop policies of reimbursement until the radiopharmaceuticals are approved by the FDA. Several carriers have stated that their reimbursement policies forbid them from paying for nonapproved techniques or drugs and, if the radiopharmaceutical is not FDA approved, it is considered experimental and not eligible for reimbursement.

Several factors have resulted in the absence of policies of reimbursement for PET scans. The early evaluations of MRI have been criticized and the demonstration of clinical efficacy has been questioned (*16,17*). Thus, PET is undergoing closer scrutiny than previous technologies. The costs of health care are consuming an increasing percentage—now estimated to be 14%—of the gross national product. All new procedures are undergoing extensive review processes, forcing prolonged delays or denials. The costs of PET studies are a factor in the lack of policies for reimbursement. Very good data demonstrating PET's cost-effectiveness would be beneficial to the attempt to obtain reimbursement, but those data are not available at this time.

Other limitations for supporting a reimbursement policy by third-party payers are the small number of clinical studies and the limited amount of outcome data reported in the literature. Only a few centers have been performing clinical studies, and frequently the reports of studies from these centers have included small numbers of patients. The studies in clinical PET are generally well done and demonstrate the utility of PET, but more studies that include larger numbers of patients would provide the reviewing agencies with better documentation of the clinical uses of PET. Another problem for PET reimbursement is the absence of a groundswell of support. If more centers were performing the studies, the centers and their doctors and patients would be requesting reimbursement.

For clinical PET to be successful, several changes will be necessary in the PET facility. The major change that must occur is increased patient throughput. Most clinical PET centers now see a few patients each day; the number of patients scannned during each 8-hr shift must be increased to 8–10 for PET to be cost-effective. The new tomographs have larger axial fields of view and transmission imaging with emission imaging, which results in improved patient throughput. Furthermore, the use of true three-dimensional imaging with the septa removed will also facilitate patient throughput.

PET's costs must be controlled. The costs for tomographs, radiopharmaceuticals, maintenance and personnel necessary for performing the studies will need to be decreased so that the costs of PET procedures are competitive with other imaging procedures.

The role of clinical PET has been discussed for several years. The imaging equipment and radiopharmaceutical industries have made large investments in developing PET technology, but their return on their investments has been meager so far. If sales do not increase, these industries may not be able to maintain their investments in this technology. Thus, if reimbursement for PET does not occur soon, clinical PET may not develop and may be relegated to the research laboratory.

In summary, PET studies have been demonstrated to provide unique clinical information important to the care of patients, but several obstacles must be overcome. A major problem for clinical PET is the FDA's position that PET radiopharmaceuticals need NDAs. Because NDAs are difficult to obtain and there is no third-party reimbursement without FDA approval of radiopharmaceuticals, clinical PET's position is threatened. If reimbursement for clinical PET is not forthcoming in the near future (1–2 yr), the industries which have invested in this technology will withdraw their investments, leaving the nuclear medicine community without access to needed technology.

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