Part I The Reinvention of PET

New technologies are enabling nuclear physicians to get PET-quality images using SPECT cameras. Positron imaging is poised to become a routine part of nuclear medicine. How will the field adapt?

Until fairly recently, PET had been viewed largely as a research tool—the crown jewel of nuclear medicine that was not available to the masses. Many insurance companies would not consider reimbursing for the imaging test that they deemed "experimental." The vast majority of U.S. teaching hospitals chose not to spend $4 million to purchase a PET system and cyclotron. In fact, only 73 PET centers existed throughout the country until recently. "To those uninformed about PET's benefits, PET represented 'high tech and high cost' and that earned it a bad name," said Ernest Garcia, PhD, president of the Institute of Clinical PET and a professor of radiology at Emory University in Atlanta, GA.

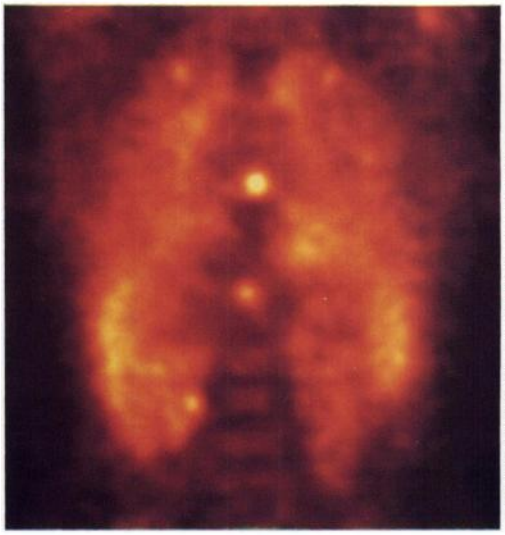
Within the past year, PET has been reinvented. Three camera companies introduced coincidence detection systems that can be added on to SPECT cameras enabling them to perform positron imaging using the PET radiopharmaceutical ^{18}F-fluorodeoxyglucose (FDG). Several researchers have also demonstrated that, in cardiac FDG imaging, SPECT with 511 keV collimators can provide a diagnostic accuracy similar to PET. Recognizing the impending increase in demand for FDG, a new pharmacy network opened six months ago and has begun supplying FDG to hospitals that do not have cyclotrons on site.

"PET is moving from the few to the many," said Garcia. "Over the next year, the number of PET centers throughout the U.S. could double as hospitals begin buying SPECT coincidence detection cameras to perform PET imaging."

This article is the first of a two-part series exploring the recent developments that are bringing PET into widespread use. The second part, which will appear in next month's *Newsline*, will focus on the lack of reimbursement and excess of regulations concerning PET procedures as well as the efforts to overcome these challenges.

New Promise for Oncology Diagnosis

During the fall 1995 Radiological Society of North America (RSNA) meeting, Horace Hines, PhD, chief technical officer for ADAC Laboratories in Milpitas, CA, received word that the Food and Drug Administration (FDA) had approved ADAC's coincidence detection camera. "At that point, we knew the image quality wasn't quite there," he said. "The camera was equipped with a ⅜-inch crystal, and we were in the process of switching over to a ⅝-inch crystal." For this reason, ADAC waited a year before it began promoting its new coincidence detection camera once the new crystal was installed. The company sold over 30 coincidence cameras in 1996 to nuclear medicine departments, according to Hines.



–Photo courtesy of ADAC Laboratories, Dr. Shreve and Dr. Wahl.

A coronal view of a middle-aged woman acquired using a coincidence detection camera with one-bed position encompassing the neck down to the iliac crest in 23 min. The coronal reconstruction reveals abnormal FDG uptake in a 1 cm left-lung nodule, 1 cm right-lung nodule, mediastinum and a nonenlarged retrocrural lymph node. These correspond to recurrent and metastatic squamous cell carcinoma. Normal structures seen include marrow activity in the spine, and soft tissue activity in kidneys, liver and spleen are discernible.

The biggest draw is the lower cost of the coincidence detection compared to traditional PET. The coincidence add-on costs $250,000 for those who already have the $700,000 SPECT camera with a digital detector. (ADAC's coincidence system will only fit on its Solus or Vertex cameras with Epic digital detectors.) Both Elscint and Picker have also recently introduced coincidence detection add-ons for their digital SPECT cameras. Picker has received FDA approval for its coincidence camera, and Elscint is awaiting approval.

In addition to lower costs, the coincidence detection add-on holds a key advantage, in that hospitals do not need to have dedicated SPECT cameras for PET imaging. "The nuclear physician can literally finish a bone scan on a patient and then switch to an FDG study by making a few adjustments," Hines said. "Our goal is to make coincidence detection imaging just another nuclear medicine procedure." Stephen M. Larson, MD, chief of nuclear medicine at Memorial Sloan-Kettering Cancer Center in New York shares this enthusiasm. "This is a tremendously valuable advance that will bring PET to more people that don't have access to it."

The widespread application of coincidence imaging, however, may trickle slowly into nuclear medicine departments. "We still need clinical validation that coincidence detection can generate images of a diagnostic quality similar to that of PET," Garcia said. "At this point, the clinical value of coincidence detection has not been estab-

lished. We will also need to train physicians how to perform and interpret these studies."

Once coincidence detection proves itself in clinical trials, "oncologic positron imaging will be the next major area of growth in nuclear medicine," said Garcia. Larson concurred and pointed out that it may be extremely useful for the evaluation of patients with solitary pulmonary nodules detected on a screening chest radiograph.

"Those patients who have benign lesions based on the scan can be followed instead of put through unnecessary surgery."

For the 130,000 patients who are diagnosed with solitary nodules every year, a thoracotomy is the only option. This is despite the fact that the nodules in half of these patients are benign. "SPECT-PET can be used before surgery to distinguish cancers from noncancers," Larson said. "Those patients who have benign lesions based on the scan can be followed instead of put through unnecessary surgery."

Larson's department at Memorial Sloan-Kettering, which has a PET system, has purchased a coincidence camera but has not yet begun to use it on patients. Larson first plans to use the coincidence system in a clinical trial. ADAC is sponsoring a multicenter clinical trial, which Larson's institution may join, to see how coincidence detection compares to surgery in the staging of lung cancer. Preliminary results should be available in August, according to Hines.

Not Quite PET

Although coincidence detection systems and 511 keV collimators may substitute well in nuclear medicine departments that do not have access to PET, they also have their limitations. For instance, they do not get as high a count rate as PET scanners. A coincidence detection camera gets an actual count rate of about 10,000 counts per second in an FDG tumor study compared to a count rate of 30,000 counts per second for PET, according to Gerd Muehllehner, PhD, president of UGM Medical Systems in Philadelphia. "To get the same image quality as a 30-minute PET study, it would take the coincidence detection study about one and a half hours," he said. The 511 keV collimators would take even longer since they have lower count rates. Practically speaking, count rates could come into play if the multifunctional SPECT camera was needed for another study.

Another major drawback of the coincidence detection systems is that the manufacturers do not offer attenuation correction. "We already have attenuation correction for our SPECT cameras in cardiac imaging," said Hines. "We have not developed attenuation correction for coincidence detection, but it's not clear whether it's really required for oncologic imaging."

Attenuation correction is, however, required for cardiac imaging. Where PET is most useful in cardiac studies is in the evaluation of heart muscle viability to determine the need for a heart transplant. Without attenuation correction, coincidence detection cameras cannot reliably evaluate these patients, according to Garcia.

A SPECT camera equipped with a 511-keV collimator, on the other hand, may offer a solution for evaluating myocardial viability. A recent study conducted by Eric Chen, PhD, at the Cleveland Clinic Foundation in Cleveland, OH, found that FDG-SPECT using a 511-keV collimator had

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Using PET to Evaluate Chemotherapy

With all the effort put into developing chemotherapeutic agents, no one knows precisely what these drugs do to tumors and healthy tissues. "We need to know what is actually happening in the tumor, not just in the plasma," said Pat Price, MD, a professor of clinical oncology at Hammersmith Hospital in London. She is working to organize a new PET study group of the European Organization for Research and Treatment of Cancer.

Price got the idea for this project about four years ago when she realized that the study of tumor response and mechanism of action of chemotherapy was not exploiting new technologies such as PET. She and her collaborators at Hammersmith have been conducting PET studies using ^{18}F and ^{11}C to radiolabel experimental chemotherapy drugs. Their goal is to see if the drugs work as they are supposed to work. This can help pharmaceutical companies determine which drugs should be taken into large clinical trials.

For example, the Hammersmith team used ^{18}F to radiolabel 5-FU, a drug commonly used to treat colorectal cancer. They used PET scans and found that certain experimental drugs could enhance the effectiveness of $5^{18}FU$. The team then studied a new class of cancer drugs called thymidylate synthase (TS) inhibitors by radiolabeling the nucleotide thymidine with ^{11}C and injecting the product into a patient receiving a TS inhibitor. "We used PET to demonstrate salvage thymidine regulation in the tumor which shows the TS inhibitor is working as it should," said Price.

She emphasized that her team is going beyond FDG and blood flow studies to determine the actual mechanism of action of drugs into tumor cells. She recently completed a pre-Phase I trial on a potential new chemotherapeutic agent in which patients were given 1/1000th of the dose that would be given in the Phase I toxicity trial. Even at that dose, PET could detect clearance of the concentration from the tumor. "We get in vivo pharmokinetic data that you can't see on an FDG-PET image," Price said. "I strongly believe that this is the way forward for PET."

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an 86% sensitivity for detecting myocardial viability compared to the gold standard PET which was considered to have a 100% sensitivity (*J Nucl Med* 1996;37:(suppl):177P). Standard SPECT had a 61% sensitivity. "SPECT using a 511-keV collimator and PET resulted in a good agreement in 90% of myocardial regions. Statistically speaking, PET and high-energy SPECT were in excellent agreement," said study co-author William MacIntyre, PhD. This study confirmed previous research conducted by Martin Sandler, MD, and colleagues at Vanderbilt University in Nashville, TN.

Even if coincidence detection is reserved mainly for oncology imaging, it remains to be seen whether artifacts will factor in diagnosing certain cancers. Garcia pointed out that with brain studies the hardware for attenuation correction is not needed since it can be easily calculated. Whether attenuation correction will be needed for breast cancer imaging, for example, is still an open-ended question. In ADAC's early trials so far using FDG and coincidence detection, "we've obtained good results for lung cancer, head and neck cancer, breast cancer, melanoma and colorectal cancer," said Hines. Coincidence detection has not been as successful with prostate cancer since prostate tumors do not always have high FDG uptakes.

An Increased Need for FDG

A determining factor in whether SPECT-PET will come into widespread use is the availability of FDG, the radiopharmaceutical used in the vast majority of PET procedures. Currently, FDG is an "orphan" drug, which means no pharmaceutical company owns it. This combined with the two-hour half-life of FDG is why PET centers have their own cyclotrons on site to produce FDG on demand. Without an on site cyclotron, hospitals that purchase coincidence detection cameras or 511 keV collimators must somehow find a way to obtain FDG.

Enter PETNet Pharmaceutical Services, a new pharmacy network that distributes FDG. The corporation was formed six months ago as a joint venture between Syncor and CTI and already has about 100 customers, according to Ruth Tesar, vice president of marketing for PETNet, which is based in Atlanta, GA. "Most of our customers are using new coincidence detection images and high-energy collimators to do FDG studies," she said.

PETNet currently has 10 sites where it produces FDG at cyclotrons owned by hospitals and universities throughout the country. "We plan to increase to 25 sites over the next three years," said Tesar.

For $750 per dose, a nuclear medicine department can obtain FDG within a day of filing an order or even on the same day in an emergency case. With the two-hour half-life of ^{18}F, customers need to be located within a 120-mile radius of a distribution site. "We have flown our shipments to customers, but this increases the price to over $1000 a dose," said Tesar.

One of the main challenges to setting up this network was getting sanctioning from the FDA. PETNet still has yet to receive FDA approval for their abbreviated New Drug Application, which would formally allow them to distribute FDG. Until they get this approval, the network is being allowed to operate under the FDA's watchful eye and with the agreement that it will work within each state's laws of pharmacy and medicine, according to Tesar.

With the new distribution network for FDG and the lower cost cameras that can perform positron imaging, nuclear medicine is on the brink of some major changes. However, the clinical acceptance of SPECT-PET may be hampered by FDA regulations and by the Health Care Financing Administration's reluctance to reimburse for the procedures. The new developments have thrust PET into the spotlight of clinical nuclear medicine. What was once largely a research tool is now facing the bureaucratic realities of the clinical world.

—Deborah Kotz

Editor's Note

As coincidence detection cameras and high-energy SPECT collimators come into widespread use, we in the nuclear medicine community need to establish terms to distinguish the new PET imaging from traditional PET. SPECT-PET is one reference I've seen. Any other suggestions?

—Conrad Nagle, MD, JNM Associate Editor

Exploring Vietnam

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French-Vietnamese restaurants.

My professional host in Saigon was Dr. Trinh Thi Minh Chau, head of the nuclear medicne department at the 1050-bed Cho Ray Hospital. This facility serves as the clinical campus for the Medical College of Ho Chi Minh City. There are five physicians, twelve technologists and six nurses as well as other basic science support personnel in the department. The monthly census of procedures consists of 200 thyroid uptake and rectilinear scans as well as 100 imaging studies performed on a MEDEX reconditioned Searle/Siemens camera-computer system. Heart, bone, liver, brain and kidney studies predominate. At the time of my visit, Dr. Chau and her colleagues had treated 20 patients with metastatic thyroid cancer with 131I.

I delivered nuclear oncology lectures at both Bach Mai and Cho Ray, which were translated into Vietnamese by one of the staff physicians. From the questions asked, it was clear that my hosts possessed fairly sophisticated knowledge about the lecture topics. This, despite the fact that they do not have ready access to books and journals from the West. I was pleased to bring several publications with me as gifts for the Bach Mai and Cho Ray physicians: These included copies of the CME syllabi from the recent SNM meeting in Denver. They were genuinely delighted.

One message that they wanted me to carry home was their strong desire to have more contact with their colleagues in the United States, Europe and other parts of the world. They would be gracious recipients of any books, journals or usable

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