Oncology Issues

ISSN: 1046-3356 (Print) 2573-1777 (Online) Journal homepage: https://www.tandfonline.com/loi/uacc20

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To cite this article: Stanley J. Grossman, Landis K. Griffeth & Paul C. Hanson (1999) PET Emerges as Clinical Oncologic Tool, Oncology Issues, 14:2, 16-20, DOI: 10.1080/10463356.1999.11904816

To link to this article: https://doi.org/10.1080/10463356.1999.11904816

PET Emerges as Clinical Oncologic Tool

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Positron emission tomography (PET), typically perceived as a potent research tool limited to academic centers, is now poised to enter the mainstream of clinical oncology. PET is similar to other nuclear medicine studies in which radiopharmaceuticals (drugs or compounds tagged with radioactive isotopes) are injected into patients to obtain images of metabolic/physiologic processes. In this way PET provides information not available from other imaging technologies, such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US), all of which depict anatomy, rather than physiology. Despite the potential for providing unique information critical to disease management, in this era of managed care and capitated contracts, a costly "new" imaging technology must prove its value with superior clinical accuracy, and in a cost-neutral or, preferably, cost-beneficial manner.

PET has demonstrated effectiveness on both counts. However, third-party payers continue to scrutinize the technology unlike any other imaging modality before as a condition for reimbursement. PET practitioners have spent nearly ten years accumulating clinical data for consideration by the Health Care Financing Administration (HCFA). Finally, approval was granted for Medicare reimbursement in January 1998; however, such approval is currently limited to the evaluation of solitary pulmonary nodules and the staging of non-small cell lung carcinoma. HCFA currently is considering broader coverage for additional oncologic applications, as strong supportive data continue to appear in the literature.

Concurrently, as the value of PET is recognized, private payers are increasingly approving PET reimbursement for a variety of oncologic applications. These factors have provided a strong impetus for expansion of clinical PET into the community.

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BASICS OF POSITRON EMISSION TOMOGRAPHY

Many clinicians do not realize that PET was developed more than twenty-five years ago, about the same time CT was in the early stages of clinical use. Since then PET has undergone many technological advances. The size and appearance of a modern PET scanner is very similar to that of a CT scanner. The basis of PET imaging is the labeling of small, biologically important molecules, such as sugars, amino acids, or even water, with positron-emitting radionuclides for injection into patients. These isotopes undergo a special type of radioactive decay, whereby their nuclei emit particles, or positrons. A positron is a positively charged electron, which travels only a few millimeters in tissue before colliding with its antimatter partner, the electron, converting their total mass into two photons of pure energy. These photons are emitted at 180 degrees apart from each other and can be detected simultaneously as "coincident" photons on opposite sides of the body. In the modern PET scanner, thousands of small detectors are oriented in a ring configuration, surrounding the patient's body. These detectors identify and localize millions of these positron-electron "annihilation" events per second by detecting these paired, simultaneous (or "coincident") photons. Computer reconstruction (comparable to that used with CT) of the acquired data permits a visual depiction of the distribution of the isotope within the tissues being imaged. Depending on the positron-emitting radiopharmaceutical used, various metabolic functions can thus be observed with PET.

Most clinically important positron-emitting radionuclides are produced in a medical cyclotron. They are very short lived, with half-lives measured in minutes. One positron emitter, fluorine-18 (F-18) has a 110-minute half-life, longer than most others. F-18 can be coupled to a chemical analog of glucose to produce F-18-fluorodeoxyglucose (FDG). Coincidentally, an important physiologic feature of most malignancies is their preference for glucose as an energy source, greater than most normal tissues. Glucose hypermetabolism can be easily tracked with FDG, thus allowing detection of many cancers and their metastases as "hot spots" on an FDG-PET whole body scan. This property has made FDG by far the most important and most widely used positron radiopharmaceutical today, although other agents, such as labeled amino acids and nucleic acids, also show great promise in oncology.

Historically, any institution performing PET required its own on-site cyclotron for production of positron radiopharmaceuticals. This

trend appears to be changing, due to the expense of the cyclotron and its operational requirement for specialized personnel.

PET IN ONCOLOGY

The first oncologic applications of FDG-PET were reported in 1982. These applications differentiated post-treatment radiation necrosis from recurrent cancer in brain tumors and scar tissue from recurrent tumor in colorectal carcinoma. Scar tissue, necrosis, and tumor mass usually appear identical on CT and MRI; however, they appear markedly different on PET, because tumor mass is glucose avid, while scar tissue and necrosis are not. Therein lies the difference between PET, which tracks physiologic/metabolic processes, and CT, MRI, and US, which require anatomic alterations for detection of malignancy.

In oncology, metabolic changes precede anatomic changes, hence the higher accuracy of PET in detecting a variety of neoplasms. While CT, MRI, and US have important roles in the field of oncologic imaging, they share multiple shortcomings. These include an inability to:

- differentiate scar or radiation necrosis from active tumor
- determine if a mass lesion is malignant or benign
- characterize enlarged lymph nodes as malignant or benign
- detect malignancy in normal-size lymph nodes or normal-appearing tissue
- evaluate early tumor treatment response.

PET can help solve these difficult clinical problems for a variety of cancer types. Those neoplasms either already approved for reimbursement or currently being reviewed by HCFA will be discussed briefly below.

Solitary pulmonary nodule. The goal after discovering a solitary pulmonary nodule (SPN) on chest radiography is to determine whether it is malignant, so that it can be treated appropriately, or benign (e.g., inflammation or scar), so that it can be simply followed over time. CT has been used historically to attempt to characterize these SPNs, but, too often, the CT results are indeterminate, prompting invasive and expensive testing with needle biopsy, thoracoscopy, or even thoracotomy. FDG-PET has proved to be far more accurate than CT or MRI in characterizing SPNs[1] and has demonstrated superior accuracy over needle biopsy at a lower cost and with no morbidity.

> ...PET's ability to produce a whole-body image allows detection of unexpected disease throughout the entire body.

Non-small cell lung cancer. Once non-small cell lung cancer is diagnosed, the next issue is to determine whether the patient is a candidate for surgical cure, based on the extent of disease. CT is routinely used for this purpose, although it is surprising to some that the Radiological Diagnosis Oncology Group (RDOG) found CT and MRI to be only about 60 percent sensitive and 80 percent specific for staging the mediastinum in such patients.[2] These disappointing results are explained by the reliance of anatomic imaging modalities on size criteria for detecting metastases, since even normal-size lymph nodes can harbor metastatic disease and since many enlarged lymph nodes are involved with benign, rather than malignant, processes. Metabolic imaging with FDG-PET consistently has shown higher accuracy in staging the mediastinum, with sensitivity and specificity results in the 90 percent range.[3] In addition, PET's ability to produce a whole-body image allows detection of unexpected disease throughout the entire body. Since accurate staging information is the crucial determinant in predicting surgical cure in non-small cell lung cancer, PET is superior in selecting the best candidates for surgery.

Recurrent colorectal carcinoma. Recurrent colorectal carcinoma is potentially curable if surgically resected while still localized. However, 80 percent of patients who undergo repeat laparotomies for apparently localized disease have additional future recurrences, presumably due to more extensive metastatic disease than was realized prior to surgery. PET has a possible role in improving on this outcome. The objective is to determine who are the best candidates for curative surgery. While CT, MRI, and US have been effective in detecting recurrent disease in the liver, they are much less accurate in

detecting metastases elsewhere in the abdomen and pelvis. In the setting of an elevated CEA (a serum tumor marker for colorectal cancer), FDG-PET has been far more accurate in discovering recurrences, even in the liver, at an earlier stage, when surgical cure is more likely.[4] Conversely, when an apparent solitary recurrence in the liver or elsewhere is discovered with an anatomic imaging modality, surgical cure is much less likely if there is unsuspected disease elsewhere. PET has demonstrated superiority over all anatomic imaging modalities in detecting such additional tumor deposits, allowing a more appropriate selection of patients with the best chance for surgical cure. Finally, as described earlier, PET is more accurate in differentiating post-treatment scar from tumor in patients with a history of rectal carcinoma and a persistent presacral "mass" after treatment,[5] a common occurrence.

Lymphoma. Like those with rectal carcinoma, non-Hodgkin's and Hodgkin's lymphoma patients are often left with a residual mass at the site of the original tumor after treatment. Anatomic imaging studies cannot differentiate post-treatment scar from residual tumor, requiring growth of the mass over serial studies to confirm residual malignancy. Unfortunately, if residual disease is present, this strategy will delay initiation of potentially curative therapy, which is most effective when started early. Clinical results with FDG-PET have been outstanding in this setting, since active lymphoma is especially FDG-avid ("hot") while scar tissue is not, resulting in an often relatively simple distinction.

Recurrent Melanoma. Comparable to recurrent colorectal carcinoma, the only hope for surgical cure of a melanoma recurrence is early discovery and resection while it is still localized. Anatomic imaging modalities have not proved accurate in staging the remainder of the body when an apparent solitary recurrence is discovered.

By providing unsurpassed accuracy in staging malignancies, PET can prevent unnecessary invasive diagnostic and therapeutic procedures.

Consequently, surgical cures of recurrent disease are uncommon. FDG-PET has demonstrated much higher accuracy in restaging these patients, thereby improving the selection of candidates for a potentially curative procedure.[6]

Brain tumors. When an enhancing lesion is discovered on CT or MRI after surgical and/or radiotherapy of a brain tumor, differentiation of radiation necrosis from recurrent tumor is typically not possible without biopsy. The avidity of recurrent high-grade tumor for FDG, in contrast to absent FDG uptake into necrotic tissue, makes PET the non-invasive gold standard for differentiating these lesions, with even greater accuracy than needle biopsy.[7] Because of the high glucose metabolic rate of normal brain tissue and the lower resolution of PET imaging relative to CT or MRI, FDG-PET has been less effective in assessing low-grade brain tumors, due to their lower metabolic rate, and in detecting cerebral metastases from distant primary sites, due to their frequently small size. Accordingly, PET is not recommended to replace head CT/MRI for initial lesion detection in such patients.

Recurrent Head and Neck Cancer. After a patient has had surgical and radiation therapy of a head and neck primary cancer, scar tissue forms and the local tissue planes become distorted. These tissue planes make follow-up with CT or MRI very difficult. When recurrent disease is finally discovered, it is often far advanced. FDG-PET has shown excellent utility in detecting recurrent disease at an earlier (and possibly curable) stage, since the recurrent lesions are usually strongly FDG avid and easily detected.[8]

ECONOMIC IMPACT OF PET

As noted earlier, a costly new technology is now required to prove its merit in the area of diagnostic accuracy as well as cost effectiveness. A dedicated PET scanner costs $1 to $2 million (depending on the model) and a cyclotron costs about $2 million. Fortunately, the growing interest in PET and the nearly

two-hour half-life of FDG have facilitated the development of centralized commercial cyclotron facilities. These central FDG suppliers can provide for the needs of multiple PET centers within several hours' traveling distance, thus sparing many new PET centers from the purchase of a cyclotron and dramatically reducing start-up and operating costs.

The average reimbursement for an FDG-PET study is about $2,000 to $2,500. How can such a costly technology be cost beneficial? By providing unsurpassed accuracy in staging malignancies, PET can prevent unnecessary invasive diagnostic and therapeutic procedures. For example, in several cases, adding an FDG-PET study for work-up of a solitary pulmonary nodule produced average cost savings of $1,600 to $2,100 per patient, including the cost of all the PET scans.[9,10] This apparent paradox is explained by the ability of a negative PET scan to prevent an unnecessary needle biopsy, thoracoscopy, or thoracotomy. Noncurative surgery (and unnecessary morbidity) also can be averted in biopsy-confirmed non-small cell lung cancer if PET documents unsuspected, inoperable, metastatic disease. The reported cost savings in this setting are $1,000 to $2,000 per patient, including the cost of the staging CT and PET scans.[11] Similar findings apply in the settings of recurrent colorectal carcinoma and melanoma, in which apparently localized metastases are often treated aggressively with surgical resection, despite a low cure rate. The reported cost savings generated by PET for recurrent colorectal carcinoma and melanoma are $2,600 and $2,200, respectively.[12] Unnecessary surgeries could be prevented and those performed could have a higher likelihood of success if better preoperative "restaging" information were obtained. Even greater cost savings should result when more widespread clinical experience allows PET to replace, rather than complement, one or more anatomic imaging studies in routine patient follow-up.

A more recent technological development in PET imaging is the modification of less expensive dual-head nuclear medicine SPECT cameras to image the 180-degree coincidence photons produced by positron decay. Such "coincidence cameras" can image FDG, though not as efficiently as dedicated PET cameras, at a purchase price of $500,000 to $750,000. They also maintain the ability to perform other standard nuclear procedures. Early data suggest that these "hybrid" coincidence SPECT cameras are almost as accurate as dedicated PET cameras for evaluating lung cancer, but much less accurate for neoplasms outside the thorax. Over time, however, technological advances will certainly improve these hybrid systems, and they will likely play an important role in positron imaging in the future.

In summary, PET is unlike other imaging modalities in the field of clinical oncology. It provides metabolic data not available with CT or MRI, thus offering a new standard for evaluating numerous malignancies. Despite the relatively high cost of each exam, PET has the potential to provide significant overall cost (and morbidity) savings in patient care by preventing unnecessary invasive diagnostic and therapeutic procedures. Third-party payers are increasingly appreciating this benefit. Finally, as the demand for PET increases, establishing a PET center should soon become more affordable, with the increased availability of radiopharmaceuticals and anticipated reduction in the cost of imaging equipment. PET has an important and expanding future in clinical oncology.

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PET IN THE COMMUNITY CANCER CENTER

by Nancy Harris

The Northern California PET Imaging Center (NCPIC) in Sacramento opened in late 1992 as a not-for-profit, freestanding imaging facility. Because of the large capital investment (approximately $7 million was required for development), NCPIC was established as a joint venture between Sutter Community Hospitals (now Sutter Medical Center, Sacramento) and Mercy Healthcare, two leading competitors in the Sacramento, Calif., market. Both institutions provided initial and ongoing capital to support NCPIC's opening and operational costs until the center could become self-sufficient.

Today, governance of the PET Imaging Center is provided by a board of directors comprised of an equal number of seats held by each of the two sponsoring organizations. Operational support and medical direction is provided through a contract with a large diagnostic and therapeutic radiology group, Radiological Associates of Sacramento Medical Group, Inc. Administration and management of the center are provided under contract with PETNet Pharmaceutical Services. NCPIC does not have any ties to major research funding, so its focus has been, and must continue to be, on clinically relevant uses of PET.

In 1998, the procedure volumes at NCPIC totaled 1,005 cases (90 percent oncology and 10 percent cardiology and neurology studies). In approximately 15 percent of the oncologic cases, unsuspected metastases were found that altered patients' medical management.

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START-UP AND DEVELOPMENT

The NCPIC was initially intended to primarily serve cardiology patients. Soon after the center opened, however, oncologists began incorporating the procedure into their management of selected cases. At the time, there was not much data regarding the benefits of this new technology on the diagnosis and management of cancer. NCPIC pioneered studies with oncology patients, comparing PET and surgery in terms of treatment and management. Three years were spent establishing the clinical validity and financial advantage of PET. NCPIC studies, as well as others, have shown that PET can be used over a wide range of applications in the field of oncology, including differentiation of malignant and benign tumors, staging, diagnosis of suspected recurrence, evaluation of response to therapy, differentiation of active tumor from post-radiation or surgical scarring. Additional research studies have shown that PET can help preserve patient quality of life and reduce health care costs by avoiding unnecessary biopsy and surgery in end-stage disease.

An extraordinary educational effort was required to introduce and integrate the new technology into the local and national medical standards of practice. Educational efforts included:

- one-on-one meetings with physicians
- presentation of data from research studies
- initiation of new research with local physicians
- participation in prospective cancer case conferences to facilitate appropriate physician use of PET
- continuing medical education presentations to local, regional, and national audiences.

Early on, PET pioneer Peter E. Valk, M.D., participated in cancer conferences to identify cases in which PET might assist in characterizing the nature or extent of disease more conclusively than other techniques (on occasion even avoiding surgery). Use of PET for specific cases also helped make clinicians more comfortable using the technology effectively.

At the same time NCPIC was working to increase physician acceptance, it recognized there was a need to secure payer acceptance and reimbursement for this new technology. It became clear that cost-effectiveness studies were as important to the future of NCPIC as leading-edge clinical studies. Significant inroads have been made in gaining payer acceptance and approval for use of PET. Within the last year, Medicare has approved PET for the initial staging of lung cancer and for the evaluation of solitary pulmonary nodule. Approval for expanded diagnostic applications in oncology is anticipated over the next two years. Development of new authorization and reimbursement policies and codes are evidence of increasing payer acceptance.

Since the inception of NCPIC, advancements in equipment design and manufacturing have greatly lowered the cost of PET imaging instruments. In addition, radiopharmaceuticals required for PET are now readily available through a national network of commercial cyclotron production centers. Together, these factors have dramatically reduced PET start-up and operating costs. Currently, cancer centers can introduce the same PET imaging services available at NCPIC for a capital investment of $ 800,000 to $1,000,000. In the future, PET will become more accessible to patients as costs decline and services expand geographically.