

DISCUSSIONS IN

Supported by an unrestricted educational grant from

GE Healthcare

www.gemedical.com

PET



CONTINUING EDUCATION FOR MEDICAL PROFESSIONALS

I M A G I N G

One copy of the article provided by CME LLC may be printed by the individual participant in connection with acquiring CME credit. No other reproduction or distribution of the article without the written consent of CME LLC.

Basic Concepts and Clinical Applications of PET and PET/CT in Oncology

By Henry N. Wagner Jr., M.D.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Summarize the physiologic mechanisms that make FDG an inherently powerful tool for diagnosing and evaluating cancer.
- Describe the operation of PET and the source of its high resolution.
- Discuss the value of PET for the diagnosis and characterization of various cancers.
- State the Medicare reimbursement status of PET imaging of cancer.

Dr. Wagner is professor emeritus of radiology and medicine at Johns Hopkins School of Medicine and a professor of environmental health sciences at Johns Hopkins Bloomberg School of Public Health.

Dr. Wagner has no significant financial arrangement or affiliation with any manufacturer of any pharmaceutical or medical device and is not affiliated in any manner with any provider of any commercial medical or healthcare profession service.

Fluorine-18 FDG-PET has led to a new approach to cancer diagnosis and care. Until recently, a cancer diagnosis led immediately to surgery, often performed in a fruitless attempt to cure the patient. Frequently, the disease had already spread to sites that were either unknown or locations where it could not be removed during surgery. Whole-body PET imaging is now used to diagnose cancer, differentiate it from benign disease, determine its spread throughout the body, establish prognosis, guide treatment and assess the effectiveness of therapy, and detect recurrent disease. What many of us consider whole-body imaging covers only the regions from the chin to the thigh. True whole-body imaging should extend from the top of the head to the soles of the feet.

The key to FDG-PET as a cancer imaging agent lies in the changes in cell metabolism that arise after normal cells become cancerous. Cancer cells regress to a more primitive evolutionary and developmental state. As a result, the source of energy for cancer cells changes from aerobic metabolism to anaerobic metabolism. The glucose that cancer cells crave was a major source of energy for bacteria and other primitive life-forms billions of years ago, before oxygen accumulated in the earth's atmosphere.

Evolution led to a more efficient way for living organisms to obtain the energy necessary for life, by progressing along a series of chemical reactions controlled by new genes that dictate serial chemi-

cal processes. Failure of these advanced metabolic pathways results in a return to the primitive state. One of the important enzymes in glucose utilization is hexokinase II, an ancient enzyme that was present in ancient bacteria. It still plays a major role in glucose utilization. This enzyme is responsible for the phosphorylation of glucose, an early step in glucose metabolism in cells.

Pioneering researchers in the late 1970s modified naturally occurring glucose by substituting F-18 for a hydrogen atom in the 2 position of the glucose molecule.¹ This new radiolabeled molecule could be transported into cells and phosphorylated by hexokinase. It was then trapped in the cells for a long period of time because further metabolism could not take place. Thus, F-18 FDG could be used to reflect the amount of glucose utilization going on any place in the body by means of PET imaging. Cancerous tissues tend to have higher FDG uptake rates than normal or even inflamed tissues.

F-18 emits positive beta particles, or positrons, when it decays. The positrons travel 1 to 2 mm in tissue before encountering an electron that triggers the emission of two high-energy (511 keV) photons that travel in almost exactly opposite directions. A ring of detectors in the PET camera can record the arrival of positrons even when they originate deep in the human body. A computer analysis of these events produces a 3D map of F-18 FDG distribution, revealing where glucose is being utilized.

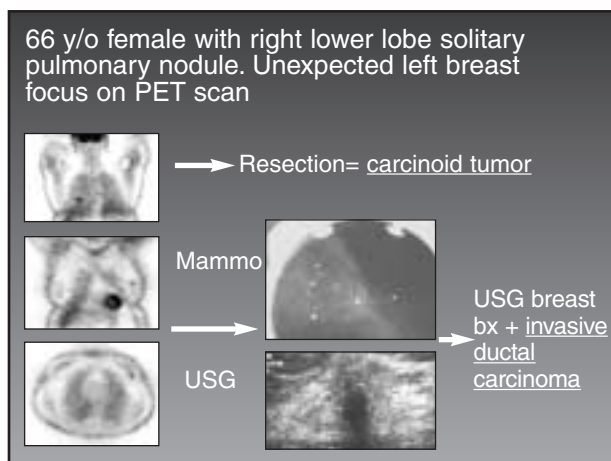


Figure 1. 66-year-old woman with right lower lobe single pulmonary nodule. Unexpected left breast focus appears on PET scan.

Using coincidence detection to localize the origin of pairs of positrons, commercial PET scanners can generate about 4-mm resolution, performance that is somewhat better than SPECT scanners used for bone and cardiac imaging.

Introduced in 2001, hybrid PET/CT scanning increases the diagnostic power of FDG-PET. Images acquired with the two modalities are fused to provide metabolic information from PET and detailed anatomic information from CT on a single set of images. The combination helps the physician determine precisely where FDG hot spots are located. The physician can more easily gauge, for example, whether a lesion resides in the lung or the chest wall.

It is likely that new radiotracers will soon become commercially available. F-18 fluoroestradiol (FES) could be useful in the identification of cancer that expresses estrogen receptors and can be treated effectively with drugs that block these receptors. F-18 fluorothymidine (FLT) could detect rapid DNA synthesis in normal areas, such as bone marrow, or rapidly dividing cancerous cells. Even in the most malignant tumors, only about 10% of the cells will be dividing over the course of the 30 minutes the FLT is accumulating. All of the cells are hypermetabolic, however, as indicated by their avid accumulation of FDG. PET imaging with FLT could provide information that enables early prediction of breast cancer's response to chemotherapy.

FDG also correlates well with response to chemotherapy.

Other candidates for commercial use as PET tracers are carbon-11 methionine and C-11 choline. Despite the fact that each has only a 20-minute half-life, hundreds of C-11

compounds can provide useful information in the care of patients.

Because tumors in prostate cancer usually involve a relatively low grade of malignancy, they do not accumulate FDG. C-11 choline is a much better tracer. The combination of CT with choline-based tracer PET is better than the use of CT alone for the detection of lymph node involvement in patients with recurrent metastatic prostate cancer. C-11 choline studies are able to differentiate between

relapse and scars that are a part of the recovery process after surgery.

Patients with cancer in the head or neck may have coexisting cancers elsewhere in the body. F-18 FDG uptake may be found in the normal ovary and uterus changes that occur with the menstrual cycle. It is important to know the menstrual phase when interpreting abdominal and pelvic F-18 FDG-PET images of women of reproductive age. Such studies should be performed within a few days after or a week before menstruation to avoid misinterpretation.

Standard uptake values with PET are used to quantify the degree of tracer accumulation. In the case of lung cancer, SUVs can vary with the phase of the respiratory cycle during the imaging. Care must be taken to ensure that breathing artifacts do not increase the statistical noise to the point that lesions may be missed. Many lesions identified with F-18 FDG may not be seen with F-18 fluoroethyl thymidine (FET).

The energy substrate for different types of cancer varies. C-11 acetate shows greater accumulation in meningioma than does FDG. This is consistent with the fact that aerobic metabolism reflects benign tumors and anaerobic metabolism is a progressive development in tumors as they become more malignant. Meningiomas, both primary and recurrent, are benign. These are characterized by low uptake of F-18 FDG and greater uptake of tracers associated with aerobic metabolism.

In patients with gliomas, fluoroDOPA may identify lesions better than F-18 FLT or F-18 FDG. F-18 FLT may become a widely used tracer, as its uptake correlates more directly with cell proliferation than does F-18 FDG, and it may be better able to demon-

strate the early effectiveness of response to chemotherapy.

CURRENT STATUS

FDG-PET is recognized as an essential part of oncology's diagnostic armamentarium. In February 2002, the Centers for Medicare and Medicaid Services expanded Medicare coverage to recognize FDG-PET's diagnostic potency for many cancer-related applications.

Its continual growth is reflected in the 218 papers and posters on oncologic applications of FDG-PET presented at the 2002 meeting of the Society of Nuclear Medicine. The total increased 175% between 1997 and 2002.

Such broadly based research over time has contributed to the versatility of FDG-PET as a cancer imaging technique. It is increasingly prescribed for examining suspected breast, cervical, colorectal, esophageal, head and neck, lung, and thyroid cancers. It plays a role in staging melanoma and staging and monitoring the effectiveness of Hodgkin's and non-Hodgkin's lymphoma treatment. FDG-PET's treatment monitoring role is expanding swiftly, and its potential as a screening tool is being explored.

- **Breast cancer.** FDG-PET reveals the preoperative extent of malignancy for patients with advanced breast cancer.² It is highly accurate for identifying locoregional lymph node metastases, although it lacks the spatial resolution to detect micrometastases and small tumor-infiltrated lymph nodes. Whole-body PET is highly accurate for detecting recurrent or metastatic breast carcinoma and useful for monitoring the tumor-shrinking effects of preoperative chemotherapy.

Medicare granted coverage for three indications relating to breast cancer in March 2002. The program began to accept billing for FDG-PET to stage breast cancer patients with distant metastases, to restage patients with locoregional recurrence or metastasis, and to monitor therapy.

- **Colorectal cancer.** Whole-body FDG-PET imaging is indicated when suspicion of recurrent tumor is found on the basis of serum carcinoembryonic antigen elevation or on clinical grounds.³ When whole-body FDG-PET is available, it should be used as the initial imaging procedure. When used as a follow-up to CT, PET is indicated for the preoperative staging of recurrent tumor that appears to be resectable, negative CT findings with rising serum CEA level, or clinical suspicion of recurrence and after an equivo-

cal abnormality is observed with CT.

Medicare has reimbursed providers since 1999 for FDG-PET studies to evaluate recurrent colorectal cancer in patients with rising levels of CEA to determine whether surgical intervention is warranted.

- **Esophageal cancer.** Esophageal cancer is rare but lethal. It is diagnosed in about 10,000 U.S. residents per year. Although the overall five-year survival rate is just 5%, skillful patient management greatly improves the possibility of long-term survival. The five-year survival rate with surgical intervention, for example, is about 30%.

Several studies have established the superiority of FDG-PET over CT for the detection of metastatic esophageal disease. Research by Luketich and colleagues demonstrated sensitivity of 69% and specificity of 93% for PET versus 46% and 74% for CT.⁴ In 1999, they concluded that 60% of patients with local disease identified with PET survived at least 30 months, compared with 20% of those who had distant disease.⁵

- **Head and neck cancer.** PET imaging can make a substantial contribution to the management of head and neck cancer.⁶ Improved detection of unknown primary and local nodal disease may alter initial therapeutic plans. Detecting early recurrence more accurately with PET may provide a means of improving the dismal survival rate from head and neck cancer recurrence.

FDG-PET can determine during initial staging whether cervical cancer cases have progressed to the lymph nodes and beyond to become metastatic disease. This determination influences decisions whether to perform either neck dissection or irradiation. By downstaging the disease, PET could help avoid unnecessary therapy. By accurately upstaging it, PET could trigger the use of appropriate therapies, thereby increasing the possibility of survival. Wong recommends the use of PET after MRI.⁷ He correctly staged 100% of patients, compared with 88% for a combined CT and PET regime.

- **Lung cancer.** FDG-PET accurately discriminates between malignant and benign solitary pulmonary nodules. Its average sensitivity in seven studies that examined its ability to characterize focal lung lesions was 95%, with an average specificity of 80%.⁸

FDG-PET uptake rates can predict patient survival. A study of 156 patients with newly diagnosed non-small cell lung cancer showed that patients with low uptake

survived significantly longer than those with higher uptake. FDG-PET is more accurate than CT for staging the mediastinum. The ranges of FDG-PET sensitivity, specificity, and accuracy are 66% to 100%, 81% to 100%, and 80% to 100%, respectively.

FDG-PET improves lung cancer case management, especially with surgical resection. Until FDG-PET, nearly 40% of patients with prescribed surgical resection to remove lesions were found to have extrathoracic lesions in the lymph nodes and elsewhere that would have precluded a surgical attempt at a cure. With FDG-PET, these cases can be identified and chemotherapy can be prescribed to avoid the morbidity and expense of fruitless thoracotomy.⁹

Since 1998, Medicare has covered the use of FDG-PET for the characterization of solitary pulmonary nodules to determine the likelihood of malignancy.

- **Thyroid cancer.** Iodine-131 remains the most widely used imaging agent in thyroid cancer, but many undifferentiated, anaplastic cancers of the thyroid do not accumulate I-131. In these cases, FDG assesses the extent of disease. Investigators at the Paterson Institute for Cancer Research in Manchester, U.K., reported at the 2002 meeting of the Society of Nuclear Medicine that combining I-124, a positron-emitting tracer, with FDG-PET to detect the broad spectrum of thyroid metastases could help plan appropriate therapy. FDG, but not I-124, is commercially available.

- **Lymphoma.** The use of targeted radionuclide therapy, particularly for the treatment of non-Hodgkin's lymphoma, promises to be a medical breakthrough equal in importance to the radio-iodine treatment of hyperthyroidism and thyroid cancer that helped hundreds of thousands of patients over the past half-century. In a series of 110 patients with various subtypes of Hodgkin's lymphoma, Dr. Abass Alavi and colleagues at the University of Pennsylvania reported 89% accuracy in detecting lesions with FDG-PET.¹⁰

Research at the University of West Virginia demonstrated that FDG-PET improves the accuracy of CT for restaging lymphoma patients after chemotherapy. In a study of 25 lymphoma patients, a

majority of the patients whose disease remitted after therapy demonstrated a significant initial decrease in FDG uptake in the first post-therapy PET study. Nine of 14 patients with significant improvement on the first post-therapy PET study went on to be disease-free for more than 12 months.¹¹

FDG-PET can help in staging the extent of disease and monitoring therapeutic results in children and adults. McNamara and colleagues found that FDG-PET modified the management of 23% of children who have lymphoma (Figure 2).¹² Initial cancer staging with FDG-PET of a 12-year-old adolescent with Hodgkin's disease uncovered unexpected bone marrow involvement. The case was upgraded from stage III to stage IV, and scheduled treatment was intensified. FDG-PET performed two months later showed adequate response to therapy, a finding confirmed by follow-up.

FDG-PET has also been used to localize hepatic metastases prior to injection of yttrium-90 contained in glass spheres called TheraSpheres to deliver radiation therapy to unresectable liver metastases.¹³

As more FDG-PET studies are performed, it becomes increasingly clear that experience and expertise help in patients with lymphoma, especially in evaluation of regions such as the spine. A homogeneous increased accumulation of FDG by itself, for example, is inadequate evidence of bone marrow involvement by lymphoma. Increased activity can be related to an increase in white blood cell count or a decrease in hematocrit. Only when marrow activity is increased and heterogeneous, focal areas of increased FDG accumulation are present can bone marrow involvement of the spine be diagnosed.

Medicare has paid for FDG-PET to stage

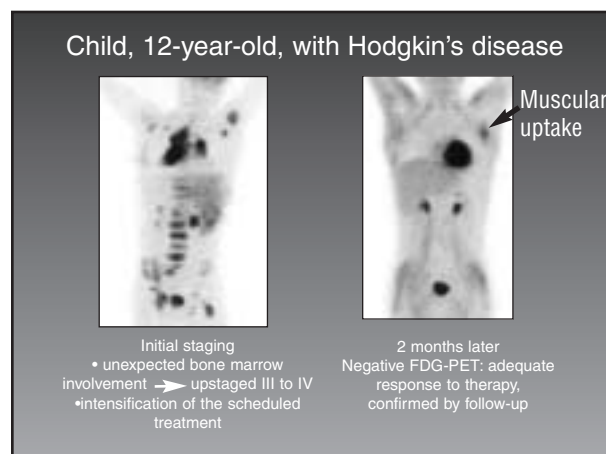


Figure 2.

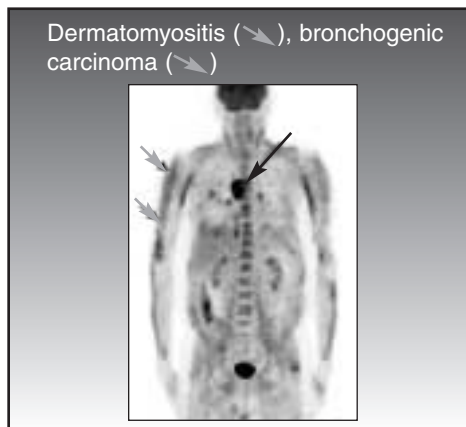


Figure 3. FDG-PET was able to detect not only skin abnormalities but also lung cancer in this patient with paraneoplastic syndrome. (Provided by Johann Wolfgang Goethe-University Hospital in Frankfurt, Germany)

Hodgkin's and non-Hodgkin's lymphoma since 1999.

- **Melanoma.** Medicare has paid for FDG-PET to detect recurrent melanoma and as an alternative to gallium scans since 1999. PET appears to be far superior to conventional CT imaging for detecting extranodal metastases during initial staging and therapy monitoring.

A University of Frankfurt study in 1998 of 100 high-risk melanoma patients found that PET outperformed conventional imaging in all but one respect. On the basis of patients, the sensitivity and specificity of PET were 100% and 95.5%, respectively, compared with 84.6% and

57.5% for conventional diagnostics. On the basis of single lesions, the sensitivity and specificity of PET were 91.8% and 94.4%, respectively, compared with 57.5% and 45% for conventional diagnostics. Although PET was significantly more sensitive to cervical and abdominal metastases, CT was preferred, for detecting small lung metastases.¹⁴

- **Screening.** In Japan, many whole-body FDG-PET studies are performed on healthy people every year. Although some unsuspected cancers are found, the \$2000 exams are too costly to be recommended.

Screening FDG-PET may be appropriate, however, for people who are at high risk for developing cancer. Recommendations for screening FDG-PET will probably increase over time as genetic screening becomes more common. To date, no data exist about the results in FDG-PET on the basis of genetically defined risk factors, but a step in this direction is the study of so-called paraneoplastic disease. Some patients with diseases such as dermatomyositis or encephalitis may have an undiagnosed associated cancer.

The patient shown in Figure 3 had dermatomyositis and was found to have a previously undiagnosed bronchogenic cancer on a whole-body FDG-PET study. This study by Berner and Associates in Switzerland was selected as the Image of the Year at

a meeting of the Society of Nuclear Medicine.

CONCLUSION

The basic technology of nuclear medicine (PET and SPECT) makes it possible to trace the biochemical processes wherever they are occurring throughout the human body. Photons emitted by radioactive tracers, such as F-18 FDG, can penetrate the tissues of the human body and be measured by radiation detectors that surround the entire body or are directed at particular regions or organs.

PET and SPECT have provided a new way to define disease in terms of abnormalities in biochemical or physiologic processes in specific regions of the body. The totality of these processes varies from person to person, and each sick person can be characterized by abnormalities in one or more of these regional biochemical processes.

In oncology, one of the most important measurements is the rate of utilization of glucose, which can be measured with F-18 FDG. Thus, the nature of the disease is defined in terms of the nature of the individual person. People can have similar components of disease, but no two patients will be the same. PET and SPECT make possible care directed to the specific patient, as distinct from care directed to the statistical characterization of his or her disease. This is indeed a revolutionary approach to the practice of medicine.

To complete this CME activity free of charge, please go to the accredited provider website www.mhsource.com/mru for post testing and Reader Evaluation. For questions about this CME activity, please contact: onlinecme@cmp.com

REFERENCES

1. Fowler JS, Ito T. Initial and subsequent approach for the synthesis of 18FDG. *Semin Nucl Med* 2002;32(1):6-12.
2. Avril N, Dose J, Janicke F, et al. Metabolic characterization of breast tumors with positron emission tomography using F 18 fluorodeoxyglucose. *J Clin Oncol* 1996;14:1848-1857.
3. Schiepers C, Penninckx F, DeVadder N, et al. Contribution of PET in the diagnosis of recurrent colorectal cancer: comparison with conventional imaging. *Eur J Surg Oncol* 1995;2:517-522.
4. Luketich JD, Schauer PR, Meltzer CC, et al. Role of positron emission tomography in staging esophageal cancer. *Ann Thorac Surg* 1997;64:765-769.
5. Luketich JD, Friedman DM, Weigael TL, et al. Evaluation of distant metastases in esophageal cancer: 100 consecutive positron emission tomography scans. *Ann Thorac Surg* 1999;68:1133-1137.
6. Lowe VJ, Boyd JH, Dunphy FR, et al. Surveillance for recurrent head and neck cancer using positron emission tomography. *J Clin Oncol* 2000;18:651-658.
7. Wong WL, Chevetton EB, McGurk M, et al. A prospective study of PET-FDG imaging for the assessment of head and neck squamous cell carcinoma. *Clin Otolaryngol* 1997;22(3):209-214.
8. Bury T, Dowlati A, Paulus P, et al. Whole-body 18FDG positron emission tomography staging of non-small cell lung cancer. *Eur Respir Journal*. 1997;10:2529-2634.
9. Oyen WJ, et al., Impact of FDG-PET on the management of primary non-small cell lung cancer. Presented at annual meeting of Society Nuclear Medicine, Los Angeles, June 2002.
10. Guan L, Zhuang HM, Alavi A, et al. Sensitivity of FDG-PET for different types of non-Hodgkin's lymphoma as defined by WHO/REAL classification. Presented at annual meeting of Society of Nuclear Medicine, Los Angeles, June 2002.
11. Gupta N, Mallidi P, Qazil M, et al. Whole body PET-FDG imaging for monitoring therapy and predicting treatment response in lymphoma patients. Presented at annual meeting of Society of Nuclear Medicine, Los Angeles, June 2002.
12. McNamara D, Montravers F, Landman Parker J, et al. [18F]-FDG-PET in childhood lymphoma: clinical utility and impact on management. Presented at annual meeting of Society of Nuclear Medicine, Los Angeles, June 2002.
13. Gates VL, Salem R, Culver-Schultz C, et al. Treatment of unresectable hepatic malignancies using TheraSphere: a team approach. Presented at annual meeting of Society of Nuclear Medicine, Los Angeles, June 2002.
14. Rinne D, Baum RP, Hor G, et al. Primary staging and follow-up of high risk melanoma patients with whole-body 18F-fluorodeoxyglucose positron emission tomography: results of a prospective study of 100 patients. *Cancer* 1998;82:1664-1671.

M05J007JAN • Release: Jan 2005 • Expiration: Jan 2008
Reviews Scheduled: Jan 2006 and Jan 2007

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of CME LLC and CMP Healthcare Media. CME LLC is accredited by the ACCME to provide continuing medical education for physicians.

Physicians: CME LLC designates this program for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the educational activity.

Radiologists: The American College of Radiology (ACR) accepts activities designated for AMA Physician's Recognition Award (PRA) category 1 credit.

Florida Residents: CME LLC is an approved provider of continuing medical education for physicians, osteopathic physicians, physician assistants, and nurses in the State of Florida and is registered with CE Broker.

Physician Assistants: The American Academy of Physician Assistants (AAPA) accepts AMA category 1 credit from organizations accredited by the ACCME
Nurses: The American Nurses Credentialing Center (ANCC) accepts AMA category 1 credit toward recertification requirements. CME LLC is approved by the California Board of Registered Nursing, Provider No. CEP12748, and designates this educational activity for 1.0 contact hours for nurses.

Activities that have been designated for AMA/PRA category 1 credit and are relevant to the radiologic sciences are accepted as category B credit on a one for one basis by the American Registry of Radiologic Technologists (ARRT). Radiologic Technicians may receive a maximum of 12 category B credits per biennium