



# DISCUSSIONS IN

## PET

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## Basic Concepts and Clinical Applications of PET in Oncology

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

### LEARNING OBJECTIVES

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

- Understand the physiological mechanisms that make FDG an inherently powerful tool for diagnosing and evaluating cancer.
- Appreciate the operation of PET and the source of its high resolution.
- Learn the value of PET for the diagnosis and characterization of various cancers.
- Gain a basic understanding about the Medicare reimbursement status of PET imaging of cancer.

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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.

**F**lourine-18 FDG-PET has created 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 in locations where they could not be removed during surgery. Whole-body PET imaging is 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.

The key to FDG-PET as a cancer-imaging agent is associated with 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 progressively evolving a series of chemical reactions controlled by new genes that control serial chemical 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.<sup>1</sup> 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. Moreover, as shown in Figure 1, 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 mm to 2 mm in tissue before encountering an electron that triggers a nuclear annihilation. This event results in 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.

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 single-photon emission computed tomography (SPECT)

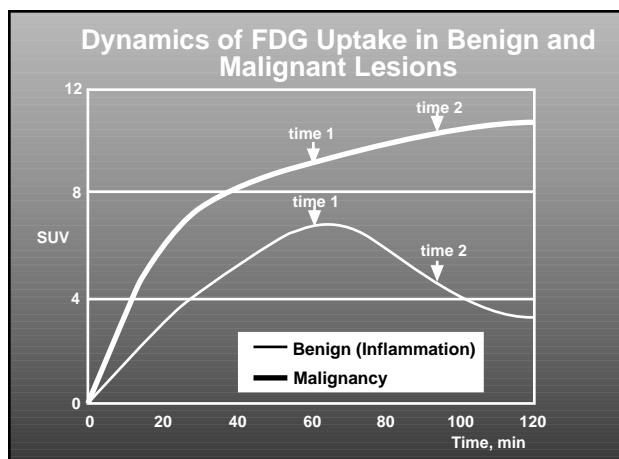


Figure 1

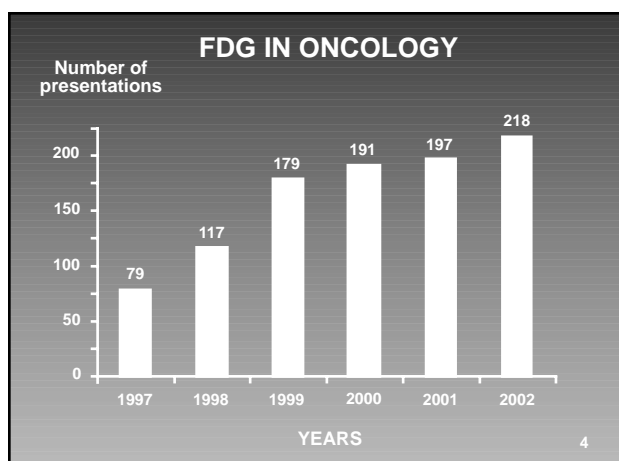


Figure 2

scanners used for bone and cardiac imaging.

Introduced in 2001, hybrid PET/CT 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, for example, can more easily gauge whether a lesion resides in the lung or chest wall.

### CURRENT STATUS

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

Its continual growth is reflected in the 218 papers and posters on oncological appli-

cations of FDG-PET presented at the 2002 annual meeting of the Society of Nuclear Medicine (Figure 2). 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 instrument. 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.<sup>2</sup> It is highly accurate for identifying loco-

regional 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 effects of preoperative chemotherapy. (Figure 3)

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 loco-regional 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 CEA elevation or on clinical grounds.<sup>3</sup> 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 carcinoembryonic antigen (CEA) level or clinical suspicion of recurrence and after an equivocal 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. citizens 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.<sup>4</sup> In 1999, they concluded that 60% of patients with local disease identified with PET survived at least 30 months compared to 20% of those who had distant disease.<sup>5</sup>

### HEAD AND NECK CANCER

PET imaging can make a substantial contribution to the management of head and neck cancer.<sup>6</sup> Improved detection of unknown primaries 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 down staging 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.<sup>7</sup> He correctly staged 100% of patients compared to 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%.<sup>8</sup>

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 imaging in 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 extra-thoracic 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.<sup>9</sup>

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

In thyroid cancer, iodine-131 remains the most widely used imaging agent, 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, England, reported at the 2002 meeting of the Society of Nuclear Medicine that combining iodine-124, a positron-emitting tracer, with FDG-PET to detect the broad spectrum of thyroid metastases to help plan appropriate therapy. FDG, but not I-124, is commercially available.

## LYMPHOMA

Just as radio-iodine treatment of hyperthyroidism and thyroid cancer has helped hundreds of thousands of patients over the past half century, the recent use of targeted radionuclide therapy, particularly for the treatment of non-Hodgkin's lymphoma, promises to be an equally important medical breakthrough. 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.<sup>10</sup> Research at the University of West Virginia demonstrated that FDG-PET improves on 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 went on to be disease-free for more than 12 months.<sup>11</sup>

FDG-PET can help in staging the extent of disease and therapeutic results in children and adults. McNamara and colleagues found that FDG-PET modified the management of 23% of children who have lymphoma (Figure 4).<sup>12</sup> Initial cancer staging with FDG-PET of a 12-year-old adolescent with Hodgkin's disease (left) 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 (right) showed adequate response to therapy, a finding confirmed by followup.

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

As more FDG-PET studies are performed, it is becoming increasingly clear that experience and expertise help, especially in evaluation of regions, such as the spine in patients with lymphoma. For example, a homogeneous increased accumulation of FDG by itself is inadequate evidence of bone marrow involvement by lymphoma. Increased activity can be related to an increase

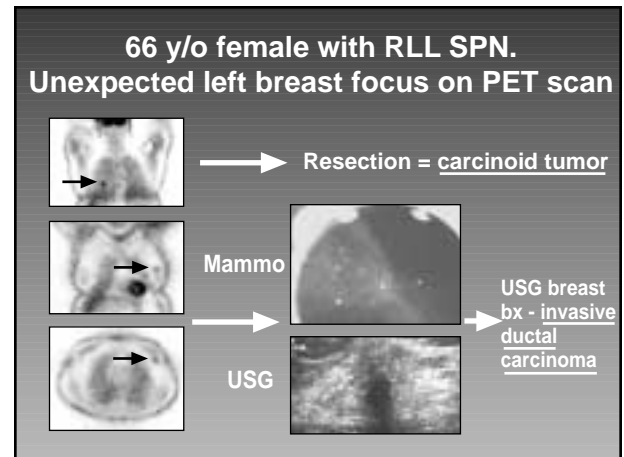


Figure 3. Sixty-six-year-old female with RLL SPN. Unexpected left breast focus on PET scan.

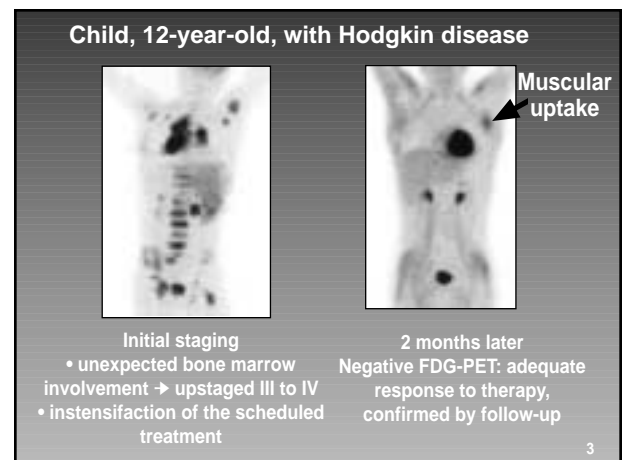


Figure 4

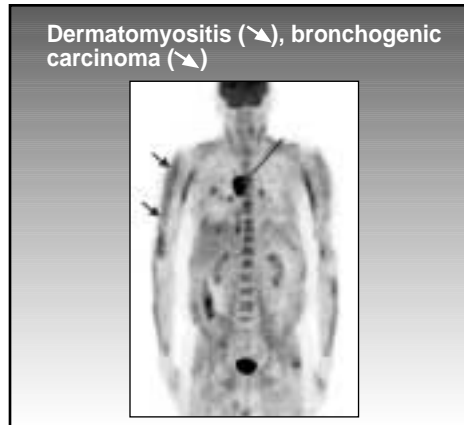
in white blood cell count, or a decrease in hematocrit. Only when marrow activity is increased and heterogeneous, focal areas of increased FDG accumulation are present can one diagnose bone marrow involvement of the spine.

Medicare has paid for FDG-PET to stage Hodgkin's and non-Hodgkin's lymphoma since 1999.

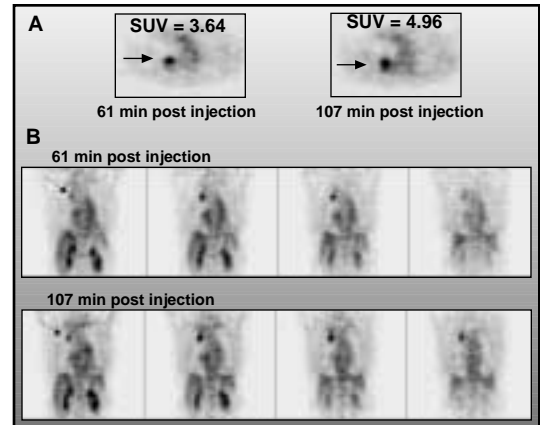
## MELANOMA

Medicare has paid for FDG-PET to detect recurrent melanoma surgery 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% compared to 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 to 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.<sup>14</sup>



**Figure 5.** 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)



**Figure 6.** FDG-PET images illustrate that malignant solitary pulmonary nodules have a higher FDG uptake rate than benign lung nodules. (Provided by A. Alavi).

**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.

However, screening FDG-PET may be appropriate for people who are of 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, at times have an associated cancer that is not diagnosed.

An example is the patient shown in Figure 5, who had dermatomyositis and was found to have a previously undiagnosed

bronchogenic cancer in a whole-body FDG-PET study. This study by Berner and Associates from Switzerland was selected as the Image of the Year at the June SNM meeting.

**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 detected and measured by detectors of radiation that surround the entire body, or are directed at particular regions or organs of the body.

PET and SPECT have provided a whole new way to define disease, in terms of

abnormalities in specific biochemical or physiological 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.

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