Review of F-18 Fluoro-2-Deoxyglucose (F-18 FDG) Positron Emission Tomography in the Evaluation of Malignancy-August 4, 1999

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I. Introduction

This is a primary medical review of F-18 fluoro-2-deoxyglucose (F-18 FDG) radiopharmaceutical used in positron emission tomography (PET) to determine abnormal glucose metabolism to assist in evaluating malignancy in patients with abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer.

Positron emission tomography radiopharmaceuticals have been evaluated and approved by the Food and Drug Administration (FDA) for use as diagnostic imaging agents. Typically, PET radiopharmaceuticals have a short physical half-life and they are manufactured using local cyclotrons or generators. In addition, many of the manufacturers of PET radiopharmaceuticals are located in hospitals and clinics, thus differing from the traditional pharmaceutical and device manufacturers that FDA regulates. In addition, many academic institutions have developed several PET radiopharmaceuticals. FDA has been working with the PET community to develop appropriate criteria and procedures to evaluate PET products for safety and effectiveness. On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (FDAMA) into law. Section 121 of FDAMA requires FDA to develop procedures under subsections (b) or (j) of section 505 (21 USC 355) for the approval of PET radiopharmaceuticals. FDA believes at this time that it could support the approval of some commonly used PET radiopharmaceuticals under section 505(b)(2) of the act (21 CFR 355(b)(2)).

There have been articles about F-18 FDG radiopharmaceutical used for oncology imaging since the 1980s. F-18 FDG PET has been approved by the FDA "for the measurement of regional glucose metabolism in human brain to assist in the diagnosis of seizures." PET allows the measurement of in vivo glucose metabolism with F-18 FDG, a positron-emitting radiopharmaceutical. Under steady state conditions, F-18 FDG is taken up by cells in competition with other sugars. Once inside cells, F-18 FDG is phosphorylated by hexokinase. This phosphorylation results in a polar entity that cannot diffuse out of the cell. The entity can be dephosphorylated to F-18 FDG by glucose 6 phosphatase, but dephosphorylation occurs slowly. The cellular concentration of F-18 FDG is

therefore closely representative of the accumulation of F-18 FDG and of the glycolytic activity of exogenous glucose. The amount that accumulates in the tissue over a specific period of time allows for the calculation of the rate of glucose uptake by that tissue. Accelerated glycolysis and decreased ability to make energy aerobically are features of malignant cells as well as epileptogenic brain cells. These features cause high rates of glucose uptake required to sustain the cells. Uptake by malignant cells is facilitated by increased expression of the glucose transporter molecules, GLUT1 through GLUT5, at the tumor cell surface. Increased levels and activity of hexokinase and other glycolytic enzymes are present in cancer cells. In cancer cells, which commonly lack or have relatively low levels of glucose 6 phosphatase, dephosphorylation of the polar entity occurs relatively slowly compared to non-cancerous cells. Use of F-18 FDG PET in oncology is based on the differential rates of glucose metabolism in benign and malignant tissues. However, F-18 FDG uptake is also accelerated during inflammatory processes, such as with infections, granulomas, abscesses, and other processes, leading to false-positive results and lower specificity. Moreover, the uptake of F-18 FDG varies greatly for different tumor types. High uptake on an image is usually associated with a high number of viable tumor cells, high expression of GLUT1 and GLUT3, and an increase in activity of several glycolytic enzymes, such as hexokinase, phosphofructokinase, and pyruvate dehydrogenase. Of note, lung cancer has among the highest expressions of GLUT1 while renal cell carcinoma has the lowest.

F-18 FDG PET scanning in oncology has several important features. It is minimally invasive, only requiring an intravenous injection. It differentiates lesions based on a biochemical process, namely increase glucose metabolism, rather than non-specific anatomical criteria (primarily size and location) provided by computerized axial tomography (CT) or magnetic resonance imaging (MRI). Finally, there are mathematical models to quantify metabolic activity and actual three-dimensional radioactive bio-distribution objectively, rather than use of visual interpretation.

For anatomical areas of focal interest already detected by another imaging modality, PET scanning of those areas can be performed to assess metabolic activity. As an example, abnormal anatomy from fibrosis can be differentiated from metabolically hyperactive malignant lesions. Or, in cases when serial tumor markers show elevation in monitored cancer patients, PET may be able to identify areas of hypermetabolic activity, allowing focused use of anatomical imaging with CT or MRI.

Localized scan allows for attenuation correction to optimize image quality. Many studies also utilized a semiquantitative measurement called the standardized uptake value (SUV). This is a ratio of measured radioactivity concentration in a lesion (or area of interest) to the estimated body tracer concentration, assuming a uniform distribution throughout the entire body volume. The use of lean body weight or body surface area, rather than total body weight, has been investigated by some because the distribution of F-18 FDG in the body is not uniform with higher uptake in muscle tissue than fat. Correction for serum glucose has also been explored. Because SUV values may change with time after F-18 FDG injection due to variable and unknown tumor kinetics related to tracer uptake, the time of image acquisition after F-18 FDG injection must be standardized across institutions to compare results. In addition, this might be problematic because the SUV from one institution will vary from another institution depending on type of scanning device.

The current Agency recommendation for evaluating the diagnostic effectiveness of radiopharmaceuticals for imaging is to conduct studies with an external reference standard of truth such as histopathology. Also, other imaging modalities can be used as active controls, such as MRI and CT. All F-18 FDG PET oncology studies that are in this review contain biopsy information to derive sensitivity and specificity as measurements of F-18 FDG PET performance in detecting malignancy. Sensitivity and specificity are diagnostic efficacy measures that are not dependent on prevalence of disease in a tested population. For this reason, this review does not discuss positive and negative predictive values of studies, as these are prevalence-dependent. Sensitivity and specificity, however, do vary depending on the test population (what types of cancer in the population, what concomitant conditions the patients have, such as diabetes, which may affect the test, etc..) Evaluating the prospective performance of a new diagnostic modality is based on the initial classification of abnormality by conventional standards. This process does not allow the new technology to assess cases that are not picked up by conventional methods such as CT or MRI. The literature has many studies of these tests' sensitivities and specificities using pathology as a standard of truth. Defining the PET study population prospectively based on abnormalities on CT, MRI, or other modalities such as chest x-ray, precludes performance evaluation of PET in patients who may be false-negatives by conventional testing. While agreement of F-18 FDG PET results with those of CT or MRI in the reviewed

studies is useful information, no attempt has been made by this review to comment on superiority of test performance. It should also be noted that comparisons between CT or MRI scans and PET imaging may not be appropriate as these other modalities provide anatomical data usually stated as size and location, as opposed to biochemical metabolic data provided by PET imaging.

This review of F-18 FDG PET literature serves as the clinical and statistical evaluation of the peer-reviewed scientific literature regarding the effectiveness and safety of F-18 FDG PET imaging for determining abnormal glucose metabolism to assist in evaluating malignancy in patients with abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer. Because of the publicly available safety and effectiveness data documenting the product's use cited in this review, safety and effectiveness requirements of section 505(b)(2) of the act (21 USC 355(b)(2)) and part 314 (21 CFR part 314) for this product and this use may be met by citing the docket number (Docket No._____) of this review.

II. Evaluation of the Effectiveness Data for F-18 FDG PET Imaging in Oncology

A. Data Sources

FDA's Center for Drug Evaluation and Research (CDER) conducted a literature search of the recent peer-reviewed, medical journals to evaluate F-18 FDG PET effectiveness data in oncology. Search criteria included: full studies (not abstracts) published from January 1990 to July 1, 1998 identified as human clinical trials with F-18 FDG in PET, written in English, found by searching on-line databases of Medline, Cancerlit, Derwent Drug File, Biosis Preview, International Pharmacology Abstracts and Embase. Review articles on F-18 FDG PET imaging were identified using the same criteria in the Cochrane Database for Systemic Reviews and Cochrane Controlled Trials Register. Finally, FDA solicited references from the PET community on F-18 FDG from any time period published in peer-reviewed journals.

The search generated about 150 articles involving clinical trials with F-18 FDG in oncology. Of these, the medical reviewer selected prospective studies that allowed comparison of F-18 FDG PET imaging results to pathology or an external reference standard. Other articles were obtained using the reference sections of the primary articles identified in the above searches. Only articles that had a study population of greater than fifty, were

controlled, prospective studies, and had enough detail about PET imaging (dosage of radiopharmaceutical, imaging acquisition, and image analysis) were included in this review. The criteria of having fifty or more subjects in a study was chosen to provide more confidence in study's estimate of PET performance efficacy. Studies with fewer patients were reviewed (but not included in this writing) and their results did not differ substantively from findings of the larger study. Single studies with more than fifty patients and multiple endpoints, such as use of F-18 FDG in managing patients who underwent different types of treatments, or evaluating outcomes for different stages of cancer, etc., were not reviewed unless there were more than fifty patients in each strata (treatment group, stage, etc.) to evaluate multiple outcomes. Moreover, the study hypothesis had to pertain to evaluating F-18 FDG PET for accuracy of anatomical definition, clinical diagnosis, or efficacy of management, therapy, or outcomes for patients. Hypotheses related to experimental investigations such as cellular growth rates, SUV exploratory data analysis, or biochemical functionality were not reviewed. Finally, if multiple articles were published by collaborating authors on the same or nearly the same data set within 12 months, the article with the larger study population was reviewed.

In all, 16 articles are included in this review of effectiveness. Since no studies with pediatric patients were found, safety and effectiveness in the pediatric population is not addressed in this review.

B. Published Literature

1. Adequate and well-controlled studies. These published trials allowed FDA to assess the effectiveness F-18 FDG PET imaging to determine abnormal glucose metabolism to assist in the evaluation of malignancy in patients with abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer by having the following components in the trial design: there was comparison between F-18 FDG PET and a "truth" standard for malignancy, namely pathology results; the study population was prospectively enrolled; the entry criteria defined the target clinical population in which F-18 FDG PET was intended to be used; there were clearly defined endpoints; detailed data on findings were presented; and there were procedures to minimize interpretation bias, such as masking (also referred to as blinding) or randomization or multiple independent readers.

Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirchner P, Valk P, Karis J, Hubner K, Delbeke D, Heiberg EV, Patz EF, Coleman RE. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol 1998;16:1075-1084.

This is a prospective, multi-center trial to evaluate the sensitivity and specificity of F-18 FDG PET imaging in evaluating solitary pulmonary nodules. The study centers were the St. Louis University Health Sciences Center, Missouri, Creighton University Medical Center, Nebraska, Good Samaritan Hospital, St. Joseph's Hospital, Phoenix, AZ, University of Iowa Hospitals and Clinics, Iowa, Northern California Positron Emission Tomography Center, Los Angeles, California, University of Tennessee at Knoxville Medical Center, Vanderbilt Medical Center, Tennessee, Duke University Medical Center, North Carolina. This study enrolled 89 patients from October, 1993 to August, 1994.

Inclusion Criteria: Consecutive patients with solitary pulmonary nodules between 0.7 cm and 4.0 cm in size were considered eligible. Lesions less than 0.7 were not included, because this was the limit of resolution of the PET scanner. The nodule had to be seen on CT and the nodule had to be considered indeterminant for malignancy by conventional modalities (chest x-ray and CT scan). The study group included 61 men and 28 women with a mean age of 63 $\pm$9.5 years.

Dose: After fasting for at least 4 hours, 370 MBq of F-18 FDG was injected intravenously and emission scans were initiated after 55 to 65 minutes.

Schema of Trial: Comparison of visual interpretation of F-18 FDG PET, semiquantitative SUV analysis, and histology to determine sensitivity and specificity.

Image Protocol: PET image acquisition and reconstruction information is presented. Transmission scans were performed for attenuation correction. Chest x-rays and chest CT imaging parameters were stated.

Visual analysis of PET was performed independently by three nuclear medicine physicians. They interpreted studies with which they were not involved clinically to ensure masking of clinical history and radiographic and CT results. PET scans were interpreted once by each of the two independent readers for a total of two independent readings per scan. PET scans were interpreted as positive or negative for malignancy. The readers were presented film copies of PET images for interpretation. Abnormalities with uptake greater than the

mediastinal blood were considered positive for malignancy. Disagreement was resolved by consensus of the two readers. Results from the readers were compared and a kappa value was calculated to assess interobserver variability. The calculated kappa was 0.95, which is excellent agreement.

Chest radiographs and CT scans were interpreted independently by pulmonary radiologists at two sites; studies conducted at one of the sites were read at the other site. The interpreting physicians were masked to clinical information of the cases. Abnormalities were graded as definitely benign (an exclusion criteria) or indeterminate. Those studies not meeting the study criteria of indeterminate were excluded (4 studies).

Semiquantitative PET analysis involved placement of circular regions of interests within the visible margins of the uptake and contained the most intense activity. Analysis was performed by a physician at each of the centers who was unaware of clinical data. Region of interest data were then sent to the study's central site, Duke University, for analysis. After correction for radioactive decay, SUVs were computed. An SUV greater than 2.5 was considered indicative of malignancy.

Primary Endpoints: Visual interpretation, SUV, histology via surgery or transthoracic needle aspiration.

Results: A total of 105 patients from 9 PET centers were thought to be eligible. Of these 8 had no pathology results, and 2 had indeterminate pulmonary nodules in regions of the lung which were not imaged by PET, 4 did not meet study criteria for indeterminant, and 2 did not have CT scan results available. Data from the remaining 89 patients were evaluated. Histopathological results of sixty of the 89 solitary pulmonary nodules were malignant and 29 were benign. (Prevalence of malignancy was 67%.) Sixty patients underwent surgery and 29 patients underwent transthoracic needle aspiration to obtain biopsy material. Individual patient data was published for all cases, which included sex, age, visual reading, SUV, size of lesion, location, and histology.

Fifty of the 60 histopathologically confirmed malignancies were primary non-small cell lung cancer. The other histopathologies were 5 cases of melanoma, and one case each of Hodgkin's lymphoma, small-cell lung cancer, malignant neural tumor, malignant carcinoid, and colon cancer metastasis. The benign findings were 7/29 granuloma, 7/29 coccidiomycosis, 4/29 benign cellular debris, 4/29 non

specific inflammation, 3/29 necrotizing granuloma, 1/29 fibrosis, 1/29 hemangioma, 1/29 aspergillosis, and 1/29 metaplasia.

Visual analysis of PET-FDG in reference to histopathology provided a sensitivity of 98% (59/60)(95% confidence intervals presented in the article: 95-100%) and specificity of 69% (20/29))(95% confidence intervals presented in the article: 957-81%). SUV data generated a sensitivity of 92% (55/60) and a specificity of 90% (26/29).

Detailed results stratified by visual and SUV analysis as well as by nodule size were provided in a table. For single pulmonary nodules of ≤1.5 cm (34 or 89 lesions) the sensitivity and specificity of SUV and visual analysis were 80% and 95% and 100% and 74% respectively.

Safety Issues: No safety issues were mentioned in the study.

Commentary: This study is a multi-centered, masked study of F-18 FDG PET visual interpretation. It also used a prospectively determined SUV as a cutoff for malignancy to determine comparative performance of SUV versus visual interpretation for F-18 FDG PET test accuracy. This study presented detailed patient information and included explanations of masking, tracking of inter-observer performance in determining regions of interests, readings done twice by independent observers per image, and CT image handling.

All patients had tissue diagnoses but the study excluded 16 patients who were originally enrolled, from the analyses. There was no long term follow-up to ensure accuracy of negatively classified subjects. In this study, the number of cancers were twice as numerous as those with benign findings, which may not fully challenge F-18 FDG PET's performance in the non-cancer patients. Finally, the confidence intervals for sensitivity and specificity were calculated by the FDA statistician using the normal theory, however, the sample size being limited, justifies use of the exact method. Using the exact method, the reported visual sensitivity of 98% has 95% confidence intervals of 91-100% and visual specificity of 69% has 95% confidence intervals of 49-85%.

Carr R, Barrington SF, Madan B, O'Doherty MJ, Saunders CAB, van der Walt J, Timothy AR. Detection of lymphoma in bone marrow by whole-body positron emission tomography. Blood 1998;91:3340-46.

This study of 50 patients performed at the United Medical and Dental Schools of Guy's and St. Thomas's, London, United Kingdom determined whether the increased marrow uptake of F-18 FDG PET observed in some lymphoma patients during routine staging PET scans represented marrow involvement by disease.

Inclusion Criteria: Fifty consecutive patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma who were staged before treatment by both PET and bone marrow biopsy were prospectively enrolled. Staging determines treatment decisions and prognosis. Routine lymphoma staging consisted of thoracic and abdominal CT scan, whole-body F-18 FDG-PET, and unilateral iliac crest marrow aspirate and trephine biopsy at this study facility. All patients had their PET scans performed within 4 weeks of the marrow biopsy.

Dose: After 6 hours of fasting, patients were injected intravenously with 350 MBq of F-18 FDG and imaged 30 to 45 minutes later.

Schema of Trial: Comparison of pathology results and PET readings.

Image Protocol: Acquisition and reconstruction were discussed, however there was no mention of attenuation correction. The intensity and distribution of the F-18 FDG activity within the marrow was visually scored by three nuclear medicine physicians independently. The marrow was assumed to be abnormal where the uptake was equal to or greater than uptake of the liver, provided the liver uptake was greater than background. The pattern of increased uptake was also noted, with patients who appeared to have focal disease only within the marrow differentiated from those with diffusely abnormal marrow changes. The kappa statistic was used to measure interobserver variability to assess the reproducibility of the visual method used to assess marrow disease on PET. Where there were differences in reporting between observers, if two reporters concurred this was taken as the final PET report.

Handling of biopsy specimens was discussed, including staining techniques, preparation, and histologic criteria. The marrow biopsy samples were examined for lymphoma infiltration by two hematologists and a histopathologist, masked to the PET scan results. Classification system was identified.

Primary Endpoints: Marrow aspirates and F-18 FDG PET results were primary endpoints.

Results: F-18 FDG PET sensitivity was 81% (13/16) and specificity was 76% (26/34) for detecting bone marrow involvement of lymphoma using unilateral bone marrow biopsy as a standard of truth. Discordant cases were discussed with pathological findings. There was complete agreement between the three observers in 76% (22/29) of scans showing normal marrow uptake and 71% (15/21) of scans showing abnormal uptake. The kappa statistic was 0.64 showing good correlation.

Safety Issues: No safety issues were mentioned.

Commentary: This study combined Hodgkin's Disease patients and non-Hodgkin's patients, which may not be appropriate as the different diseases have different estimates of bone marrow involvement in untreated patients. (Also see Moog, 1998.) This study provided details about histology evaluation and interobserver variation of interpretations of F-18 FDG PET. The study's protocol involved masking pathologists and 3 independent readings by nuclear medicine physicians. The study stated the criteria used for visual interpretation of increased F18 FDG uptake. The study did not present 95% confidence intervals for sensitivity and specificity, therefore these values were calculated by the FDA statistician. Using the exact method, the reported visual sensitivity of 81% had 95% confidence intervals of 54-96% and visual specificity of 76% had 95% confidence intervals of 59-89%. No long-term follow-up was mentioned as a means of ensuring accuracy of negatively classified patients. The study also suggests that low-grade non-Hodgkin's lymphoma may have no increased F-18 FDG uptake. Therefore, more studies are needed.

2. Supportive studies. These studies supported the use of F-18 FDG PET for determining abnormal glucose metabolism to assist in evaluating malignancy in patients with abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer. These studies may not have been masked to other imaging modalities or had main hypotheses different from evaluating F-18 FDG PET accuracy (such as determining retrospectively optimal SUV for receiver operating characteristic curves).

Avril N, Dose J, Janicke F, Sense S, Ziegler S, Laubenbacher C, Romer W, Pache H, Herz M, Allgayer B, Nathrath W, Graeff H, Schwaiger M. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. J Clin Oncol 1996;14:1848-57.

This study of 51 women was conducted at the Universitat Munchen, Munich, Germany. The purpose was to evaluate the diagnostic value of PET in differentiating between benign and malignant breast tumors.

Inclusion Criteria: Patients with abnormal mammography or palpable breast tumors who were scheduled to undergo surgery were eligible for enrollment. Patient selection was based on the availability of PET imaging. Patients were excluded based on pregnancy, diabetes, or younger than age 18. Patients with prior history of breast surgery within the last 3 months, as well as those with chemotherapy or radiation therapy, were excluded. Fifty-one women were enrolled in the study.

Dose: After fasting for at least 4 hours before PET imaging, patients were intravenously injected with 270-390 (about 10 mCi) of F-18 FDG. Patients were studied in the prone position with foam rubber well for each breast. Emission scans were obtained from 40-60 minutes after injection.

Schema of Trial: Fifty-one patients underwent PET imaging with qualitative image analysis before exploratory surgery. Quantitative image evaluation using SUV was performed using PET images identified with regions of interest placed over all histologically proven breast lesions to determine regional F-18 FDG uptake. Only tumors greater than 1 cm in diameter were included in quantitative analyses. The analyses were presented by tumor data, not patient data.

Image Protocol: Emission data was corrected for dead time and attenuation. Reconstruction was described. For quantitative analysis, regions of interests were drawn retrospectively as circles exactly around the histologically determined tumors to calculate SUV. For lesions that appeared with focally increased tumor, the circle was drawn exactly around the tumor. Reproducibility of circle positioning was studied in a subset of 20 patients with a correlation coefficient for interobserver variability of r=0.91. Intra-observer variability was 0.96. For lesions that could not be clearly identified by increased FGD activity, the surgeon's report was additionally used to position the circle. Partial volume correction was used for lesions with focally increased F-18 FDG uptake using the tumor size obtained from histologic examination. For qualitative analysis, two observers without information on the patient's clinical history or prior clinical or technical examinations visually analyzed PET images. Suspected areas of abnormal F-18 FDG uptake in breast tissue

were recorded. Regional uptake was classified using 3 categories: unlikely, probable, or definite malignant tissue. If regional F-18 FDG uptake was within the background activity of normal breast tissue, PET scans were considered as unlikely. In cases of focally marked increased F-18 FDG uptake, the scans were read as representing malignancy. All PET scans with diffuse or moderately focally increased F-18 FDG uptake were considered as probable malignant tissue. A consensus interpretation was reached for each patient.

Primary Endpoint: Qualitative visual analysis of PET images was performed. SUV were calculated for all histologically confirmed breast tumors. Only tumors greater than 1 cm in diameter were included in SUV analysis. The ability of F-18 FDG to differentiate between benign and malignant breast tumors was determined by calculating the areas under the receiver operating characteristic curve based on quantitative F-18 FDG SUV and partial-volume corrected SUV for tumors greater than 1 cm. One pathologist using World Health Organization classification analyzed all tissue specimens.

Results: In 51 patients, a total of 72 breast tumors were confirmed by histology, including 41 breast cancers and 31 benign breast tumors. Size of tumors ranged from 0.3 to 9.0 cm, with a mean diameter of 2.5 cm. Pathology findings included: for benign tumors, 23 mammary dysplasia (75%), 5 fibroadenoma (16%), 1 each of ductal adenoma, fat necrosis, and inflammatory tissue (3% each); for malignant lesions, 3 in situ carcinoma (7%), 25 invasive ductal carcinoma (25%), 9 invasive lobular carcinoma(22%), 4 miscellaneous breast carcinoma (10%).

On visual interpretation by physicians, PET had a sensitivity of 83% (34/41) and a specificity of 84% (26/31) if "probable malignant" readings were classified as positive.

Using quantitative analysis, malignant tumors (n=41) had a mean SUV of 3.3 $\pm$1.8 (range 0.4 to 9.5), whereas in benign breast tumors (n=31), the mean SUV was 1.4$\pm$0.5 (range 0.3 to 2.3). This difference was statistically significant ($P<0.01$). Receiver operating characteristic curve analysis exhibited a sensitivity of 75% and a specificity of 100% at a threshold SUV of 2.5. Sensitivity for detection of small breast cancers (less than 1 cm in diameter) was limited.

Safety Issues: There was no mention of adverse events reported with F-18 FDG administration.

Commentary: This study had 51 patients with 72 lesions undergoing biopsy. The data are presented by lesions and not analyzed by patient. The numbers of benign and malignant lesions were fairly comparable, allowing for F-18 FDG PET assessment over a spectrum of breast lesions. There was partial masking of the readers during the quantitative assessment of SUV in order to capture regions of interests that correlated with histology. Visual interpretation was performed under masked conditions.

Bury T, Dowlati A, Paulus P, Corhay JL, Hustinx R, Ghaye B, Radermecker M, Rigo R. Whole-body 18-FDG positron emission tomography staging of non-small cell lung cancer. Eur Respir J 1997;10:2529-2534.

This study from Liege, Belgium is a prospective study of 109 patients to compare the accuracy of whole-body F-18 FDG PET and conventional imaging methods for the staging of non-small cell lung cancer.

Inclusion Criteria: Between September 1994 and October 1996, whole-body F-18 FDG PET and conventional imaging methods using chest and abdominal CT and bone scans were performed to determine tumor staging in 141 consecutive patients with newly diagnosed non-small cell lung cancer. If a lesion was suspected by bone scan, confirmation was obtained by bone x-ray. The analysis was performed on 109 patients who had all test modalities and final histology results. There were 77 men and 32 women (mean age 64, range 44-83).

Dose: 200-300 MBq F-18 FDG was injected by way of an *antecubital vein in patients in a fasting state* (the length of fasting was not stated) and images were obtained 60-90 minutes after injection.

Schema of Trial: Comparison of pathology results to PET readings and conventional imaging modalities for metastatic work up (bone scan and CT).

Image Protocol: Acquisition and reconstruction of images was described in the study, however, attenuation correction was not specifically mentioned. PET data were analyzed by visual interpretation of coronal, sagittal, and transverse slices alone and in cross-referenced situations. When PET or conventional imaging study suggested mediastinal or extrathoracic metastatic disease, confirmation was obtained by biopsy or standard radiological follow-up. For PET images, nuclear physicians evaluated the images. When F 18

FDG PET uptake increase was observed, two levels were identified in comparison with normal activity: moderate (more or less twice the activity in a contralateral or reference region) or intense (markedly higher than the reference activity). These two levels of activity were considered positive for metastasis. PET and conventional imaging were interpreted separately and the results were than compared to each other and in certain cases, with the histologic information.

Bone scans and CT images were read independently by two nuclear medicine physicians and by two radiologists respectively. These readers had no knowledge of the histological diagnosis of the primary tumor. When the two readers did not agree, they reviewed the images together to reach a consensus.

Primary Endpoints: Surgical specimens were obtained within 21 days of the first of two examinations (PET or conventional imaging) in all patients. PET visual interpretation and conventional imaging interpretations were also primary endpoints. Mediastinal status and metastasis status were analyzed.

Results: One hundred nine patients had thoracotomy (61 patients), nodal biopsy of a distant site (39 patients), mediastinoscopy (5 patients), and in four patients the primary tumor invaded mediastinal structures and were classified as T4 although they did not have distant metastases and did not undergo surgical verification. In the absence of imaged metastatic disease, patients were evaluated regularly by imaging and absence of clinical disease for 6 months after negative imaging was accepted as evidence against metastasis. Final staging was: stage I, 32 patients; stage II 8 patients; stage III 30 patients; and stage IV 39 patients.

For mediastinal staging, only 66 patients underwent invasive exploration of the mediastinum. F-18 FDG sensitivity was reported as 89% (95 confidence limits 72-96%) and specificity 87% (71-96%) for these 66 patients. For CT, the sensitivity was 79% and the specificity was 71%.

For metastasis evaluation for all 109 patients, PET had a sensitivity of 100% (91-100%) and specificity of 94 % (86-98%). CT had a sensitivity of 82% and a specificity of 86%.

Safety Issues: No safety issues were mentioned.

Commentary: The study mentions that brain metastasis were not routinely assessed because it required a dedicated brain acquisition and prolonged the procedure by 20-30 minutes. The study did not mention how many readers read each PET image, whether readers were masked, whether inter- and intra-variability of interpretation were tracked, and how F-18 FDG PET images were evaluated. Confidence intervals for sensitivity and specificity presented in the study reflect acceptable performance. Nevertheless, the vast majority of patients had histological data obtained and the performance of F-18 FDG PET could be evaluated for mediastinal (local regional metastasis) and distant metastasis detection.

Delbeke D, Martin WH, Sandler MP, Chapman W, Wright Jr K, Pinson W. Evaluation of benign vs malignant hepatic lesions with positron emission tomography. Arch Surg 1998;133:510-516.

This study included 97 patients and was performed at Vanderbilt University Medical Center in Nashville, Tennessee. The main purpose was to assess the value of F-18 FDG PET to differentiate benign from malignant hepatic lesions.

Inclusion Criteria: One hundred ten consecutively referred patients with hepatic lesions 1 cm or larger on screening CT scan who were seen and evaluated for potential resection underwent PET imaging. There were 60 men and 50 women with a mean age of 59 ±14 years.

Dose: After at least 4 hours of fasting, intravenous administration of 370 MBq (10 mCi) of F-18 FDG was performed, then emission scan began 68 ±33 minutes (mean ± SD) later.

Schema of Trial: F-18 FDG PET scan and biopsy, surgery, or both were performed to assess sensitivity and specificity.

Image Protocol: Image acquisition was described including attenuation correction methods. All PET images were correlated with a CT scan of the abdomen to provide localization of lesions. However, the investigators were unaware of the previous interpretation of the CT scan. The PET images were interpreted visually, and the F-18 FDG uptake in the lesions classified as follows: poor (same or less than liver background), equivocal (mildly increased compared with normal liver background), or definite for malignancy (more than twice the radioactivity of normal liver background). The images were also analyzed

semiquantitatively using both the lesion to-normal liver background (L/B) ratio and the SUV. Regions of interest suspect for malignancy measuring 1.0 +0.5 cm2 (mean ±SD) were drawn over the areas of maximum activity within the lesion. The region of interest for the liver background was placed in a normal area of the liver.

Primary Endpoint: Endpoints were PET scan imaging interpretation, biopsy or surgery results (providing pathological samples within 2 months of PET imaging), and SUV and L/B ratio. Correlation of these endpoints was determined.

Results: On histopathology, there were 97 patients with malignant lesions (6 of these 97 patients also had benign lesions) and 13 patients with 15 benign lesions. The malignant lesions included metastases from colon cancer (n=53), pancreatic cancer (n=3), esophageal cancer (n=1), cancer of unknown origin (n=6), sarcoma (n=2), and adenoid cystic carcinoma of the parotid (n=1) in 66 patients, cholangiocarcinoma in 8 patients, and hepatocellular carcinoma in 23 patients. The benign lesions were 2 adenomas, 3 fibronodular hyperplasia, 1 cavernous hemangioma, 1 biliary cyst, 1 simple cyst, 1 hamartoma, 1 hematoma, 6 regenerating nodules, 4 benign postoperative sites, and 3 granulomatous abscesses.

Visual interpretation of F-18 FDG PET yielded readings of 87/97 (90%) malignant lesions and 22/23 (96%) benign lesions.

The SUV for malignant lesions was 7.8±4.5, significantly higher than that obtained for benign lesions (2.0 ±1.7; P<0.001).

Safety Issues: No adverse safety events were reported.

Commentary: There were more malignant lesions than benign lesions in this study, suggesting FDG PET's ability to differentiate benign from malignant lesions may not have been fully tested. Nevertheless, viewed in conjunction with Schiepers (1995) (see page 30), the specificity of F-18 FDG PET in liver evaluation is supported. All patients had pathological diagnoses. CT scan was used for localization purposes in this study and while CT interpretations were not provided, this may have biased readers. Ideally, sequential unmasking may be useful in future protocols. However, in clinical practice, radiologists would be able to use data from all previous diagnostic testing when interpreting PET, so use of CT scans in this study in consistent with intended

use of PET. There is no statement about how many readers read each PET image, or how inter or intra-variability was tracked.

Dietlein M, Scheidhauer K, Voth E, Theissen P, Schicha H. Fluorine-18 fluorodeoxyglucose positron emission tomography and iodine-131 whole-body scintigraphy in the follow-up of differentiated thyroid cancer. Eur J Nucl Med 1997;24:1342-48.

This study of 58 patients was conducted at the University of Cologne, Germany. F-18 FDG PET, I-131 whole-body scintigraphy, and pathology were compared in patients with a diagnosis of thyroid cancer.

Inclusion Criteria: Fifty-eight consecutive, unselected patients (43 women, 15 men; aged 19-72 years, median 45 years) with differentiated thyroid cancer underwent thyroidectomy and radioiodine ablation or radioiodine therapy. Forty-five of the 58 patients had received the first I-131 application for ablation of thyroid remnants 3 months previously. The other 13 patients were examined 6 months to 2 years after radioiodine ablation. Patients with a papillary micro-carcinoma or diabetes mellitus were not included in the study. From February 1995 to May 1996 FDG PET, I-131 whole-body scan, MRI, and ultrasound of the neck examinations were carried out, along with thyroglobulin levels. All examinations were carried out within the same week.

Dose: After fasting over 12 hours, with blood glucose levels before PET scans below 100 mg/dl, emission scans were obtained. Then a dose of 370 MBq F-1 FDG was injected intravenously. The study did not state what time elapsed prior to acquisition of emission scans.

Schema of Trial: F-18 FDG interpretative results were compared to I-131 results and histologic diagnosis.

Image Protocol: All imaging studies (I-131 whole body scans and F-18 FDG PET, and others) were evaluated prospectively by two experienced observers without knowledge of prior examinations. Any disagreement was resolved by consensus.

Primary Endpoints: F-18 FDG PET scan interpretations, I-131 interpretations, and histology.

Results: Thirty-eight patients presented with papillary carcinomas, 15 patients with follicular carcinomas, and five

patients with variants of follicular carcinoma. For the detection of metastases, F-18 FDG PET was found to have a sensitivity of 50% (14/28) and a specificity of 97% (29/30). For I 131 whole body scans, the sensitivity was 61% (17/28) and specificity was 100% (30/30). If F-18 FDG PET had been limited to patients with an elevated thyroglobulin level in hypothyroidism (after thyroid stimulating hormone (TSH) suppressive therapy withdrawal) and a negative I-131 scan, then the complete status would have been diagnosed correctly in 23 of 28 patients.

Safety Issues: No safety issues were reported.

Commentary: This study did not present detailed information on the imaging protocol, interpretative criteria, how masking was done in relation to different imaging modalities, and information about how pathology data were acquired. F-18 FDG sensitivity was lower than I-131 scan sensitivity. Post-hoc analysis revealed a greater sensitivity in patients with elevated thyroglobulin level when hypothyroid after TSH suppression withdrawal and a negative I-131 scan, but this was not part of the original hypothesis.

*Friess H, Langhans J, Ebert M, Beger HG, Stollfuss J, Reske SN, Buchler MW. Diagnosis of pancreatic cancer by 2[18-F]-*fluoro-2-deoxy-D-glucose *positron emission tomography. Gut 1995;36:771-777.*

This study of 80 patients and 10 controls from the University of Berne, Switzerland and the University of Ulm, Germany was a masked study to evaluate the ability of F-18 FDG PET to confirm the presence of cancer in patients with histologically confirmed pancreatic cancer and to define its specificity in patients with histologically confirmed chronic pancreatitis.

Inclusion Criteria: All patients admitted to the hospitals for elective pancreatic surgery and consented to the study were included. Eighty patients entered the prospective trial between February 1992 and November 1993. In addition, 10 controls (patients without gastrointestinal disease) were enrolled.

Dose: Patients were injected intravenously with 250-350 MBq after fasting for at least 6 hours. Acquisition and image reconstruction was presented. The patient was injected intravenously with furosemide (20 mg) and was instructed to urinate as often as possible to avoid unnecessary exposure of the bladder and to reduce measurement artifact caused by

radioactivity in the urinary collection system. Forty-five minutes after F-18 FDG administration, emission scans were recorded.

Schema of Trial: Comparison of interpretations of F-18 FDG PET images, SUV, and histology results to determine sensitivity and specificity and receiver operating characteristic curve.

Image Protocol: Transmission scans were recorded to permit correction for photon attenuation. In preliminary studies without diuretic, image quality was reduced. This data was not presented in the study. The patients had to leave the measurement area to urinate. Upon return they were carefully repositioned in the gantry using laser-supported markings. The authors estimated this led to a misalignment of a maximum of 1 cm in all directions, which in turn would cause an error of ±20% in the calculation of SUV assuming a change of 2cm in the diameter of the target volume. Images of transverse, coronal, and sagittal slices were evaluated by two independent observers who had no prior knowledge of the patients' clinical status. Pancreatic cancer was assumed if an intense focal activity accumulation was detected in the pancreatic region that exceeded the activity concentration in the liver. Circular regions of interest were drawn on the hot spots of the pancreas, corresponding regions of the head of the pancreas in patients without focal pancreatic activity, and the control regions. The size of the circles was about 1500 pixels. SUV was calculated. Additional control regions in the skeletal muscle group of the back were chose for the calculation of tumor/background ratios.

CT scans were performed between 4 and 14 days before surgery. There was no statement on how these images were handled.

Primary Endpoint: Sensitivity and specificity of F-18 FDG for detecting pancreatic cancer in suspicious patients. Comparison of CT results to PET and histology.

Results: Group I was comprised of 42 patients (30 male and 12 female; median age 60.5) with pancreatic cancer histologically confirmed at the time of surgery. Group II was comprised of 6 patients (3 male and 3 female; median age 58.5) with periampullary cancer histologically confirmed at the time of surgery. Group III had 32 patients (27 male and 5 female; median age 50) with chronic pancreatitis confirmed by pathology. The 10 controls did not have surgery. No correlation between F-18 FDG uptake (SUV) and tumor/background ratio with plasma glucose was found. Follow

up in patients with chronic pancreatitis (7-25 months) after surgery did not disclose any false diagnosis.

F-18 FDG PET identified 41/42 patients with pancreatic cancer and 4/6 with periampullary carcinoma, giving an overall sensitivity of 94% for detection of pancreatic cancer. There were 3 false-negative PET scans in this group of 48 patients with cancer. F-18 FDG scans were read as negative for cancer in 28/32 patients who had chronic pancreatitis, giving a sensitivity of 88%. The remaining 4/32 were read as false-positive. The standard uptake value of the patients with pancreatic cancer was significantly higher than for patients with chronic pancreatitis (3.09 $\pm$2.18 versus 0.87$\pm$0.56 SUV, $P<0.001$) but the difference between cancer patients' mean SUV (3.09 $\pm$2.18 SUV) and controls' SUV (0.73 $\pm$1.02 SUV) was not statistically significant, as the standard deviation for the ten controls is wide.

CT scan identified 33/42 patients with pancreatic cancer and 2/6 with periampullary carcinoma, giving an overall sensitivity of 73%. CT had a specificity of 69% (22/32).

Safety Issues: Radiochemical purity was 98.5% $\pm$0.7%, the specific activity was greater than 10,000 Ci/mmol. No other safety issues were mentioned.

Commentary: The selection of subjects was appropriate. The controls were patients with chronic pancreatitis. This diagnosis is the leading differential diagnosis for patients with suspected pancreatic carcinoma. The patients all had pathological diagnoses to correlate with imaging results. F-18 FDG performance in differentiating these controls from cancer cases is important to define and the study results show acceptable accuracy. Masking was performed for qualitative interpretation. Reading methodology was not well-described for the 2 independent readers and there was no evaluation of inter- and intra-observer variability for PET images and CT interpretations. The study did not present 95% confidence intervals for sensitivity and specificity. A detailed line listing of all 80 patients was provided with demographic data, stage (if applicable), CT, PET SUV, tumor background ratio, and operation performed were presented in the study. The study also commented that in preliminary data that were not presented, without diuretic treatment there was poor image quality and analysis because of the urinary system collection of excreted F-18 FDG. More data on use of furosemide and its potential affect on F-18 FDG imaging is needed because of it's known affects on serum glucose levels and glycolysis.

Gupta NC, Maloof J, and Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. J Nucl Med 1996;37:943-948.

This study was conducted at the West Virginia University Hospital to assess radiographically indeterminant pulmonary nodules for malignancy in 61 patients.

Inclusion Criteria: Sixty-one patients (16 women, 45 men; aged 24-89; mean age 65) presented for evaluation of indeterminant solitary pulmonary nodule 0.6-3.0 cm in size. With the exception of one patient, all solitary pulmonary nodules were noncalcified and considered indeterminant on the bases of the prior tests.

Dose: After fasting for at least 4 hours prior to PET imaging, 10 mCi of F-18 FDG was intravenously injected and image acquisition began one hour after injection.

Schema of Trial: Determination of sensitivity and specificity of F-18 FDG PET.

Image Protocol: All patients had chest x-rays and thoracic CT scans that were interpreted independently before the PET study. Transmission scanning was performed prior to F-18 FDG administration for attenuation correction. All subjects underwent two acquisitions to include the entire lung in the field of view. Images were analyzed qualitatively using visual analysis for focal areas of increased F-18 FDG uptake in both lungs' field and mediastinum by two experienced observers. Images in the transverse, coronal and sagittal vies were reviewed for the presence of focal abnormalities. The emission images were also superimposed over transmission scans for anatomic correlation. Semiquantitative analysis, to compute the SUV, was performed in all patients by drawing a region of interest 0.8cm2 over the solitary pulmonary nodule on the transaxial images. The interobserver variability to calculate SUV by drawing circles for regions of interests was <5%. Average counts per pixel in the region of interest were used to compute the SUVs. The circle was drawn over the hottest region in the nodule. In some patients, no nodules could be detected on the PET scans, so the circle was drawn in its location as extrapolated from the chest x-rays or CT scans. The counts were normalized to the patient's body mass and the injected dose.

Primary Endpoints: Final diagnoses were established by obtaining tissue from thoracotomy (n=43), percutaneous transthoracic needle aspiration biopsy (n=13) or

bronchoscopy (n=4). One subject who showed no change in nodule size for a period of 2 years was presumed to have a benign nodule.

Results: Forty-five patients had malignancies. Forty-two of the 45 patients had a diagnosis of bronchogenic carcinoma (22 adenocarcinoma, 9 squamous-cell, 7 non-small cell, and 4 small-cell). There were also 2 patients with melanoma and one with a teratoma. Six of the 61 patients had a prior history of cancer (2 breast, 2 melanoma, 1 prostate, and 1 lung). Five of these 6 patients also had malignant solitary pulmonary nodules.

Histology revealed benign lesions in 15 patients; one patient was presumed to have a benign lesion after 2 years of follow up. The benign lesions included 6 granuloma, 4 histoplasmosis, 2 nonspecific inflammation, 1 carcinoid, and 1 pneumonia. The carcinoid nodule was included in the benign group because on follow up, the clinical behavior of the carcinoid nodule was benign.

Using qualitative analysis, 42/45 (93%) malignancies were identified by PET (there were 3 false negatives) and 14/16 (88%) benign lesions were identified (there were 2 false positives).

Semiquantitative SUV indices ranged from 0.12 to 3.38 in benign nodules. For malignant nodules the values were 0.9 to 13.11. The mean values for benign nodules was 1.15 $\pm$0.98 as compared to 6.28 $\pm$3.247 in malignant nodules. This was a statistically significant difference.

Safety Issues: No safety issues were mentioned in the study.

Commentary: All patients except one had a diagnosis based on tissue specimens. While the numbers of benign cases were fewer than malignant cases, taken with the other lung cancer studies, the estimation of specificity of F-18 FDG PET is supported. The study made attempts to study inter-observer variation in identifying delineating regions of interest. For qualitative F-18 FDG PET image assessments, the readers were not masked to findings of conventional imaging evaluation. They were masked to histologic data. SUV data was determined retrospectively. This study, along with Lowe (1998), support the use of PET in evaluating indeterminant chest x-rays and CT scans of solitary pulmonary nodules.

Holder Jr. W, White RL, Zuger JH, Easton Jr. EJ, Greene FL. Effectiveness of positron emission tomography for the

detection of melanoma metastases. Annals of Surg 1998;227:764-771.

This study of 76 patients from Carolinas Medical Center, North Carolina determined the sensitivity and specificity of F-18 FDG total body PET scanning for the detection of metastases in patients with malignant melanoma.

Inclusion Criteria: The first 103 PET scans at the site done on 76 non-randomized patients having AJCC stage II to IV melanoma were included. Sixty-three of the 76 patients were derived from an immunotherapy protocol, which required whole-body PET, CT (oral and IV contrast) and MRI for staging. The remaining thirteen patients had PET, CT, and MRI for clinical evaluations, but were not part of a protocol. There were 52 males and 24 females; mean age was 55.1 years (range, 26 to 81). Histology or cytology was obtained on at least one lesion in patients with positive CT or PET scan. Patients with a fasting glucose value of over 100 mg/dl were excluded or restudied after appropriate diabetic treatment.

Dose: After a solid food fast of at least 4 hours, patients were hydrated with 16 to 24 ounces of water within 4 hours before the examination. An intravenous adapter was placed into the patient for intravenous injections of F-18 FDG and furosemide. All patients were given 10 mg of oral diazepam before the F-18 FDG injection to reduce potential muscle activation artifacts. A dose of 444 to 740 MBq (12 to 20 mCi) of F-18 FDG was given using the PRN adapter. At the end of 50 minutes, 10 mg intravenous furosemide was administered to reduce excessive renal and bladder activity. After voiding twice in the next 20 minutes, the emission images were acquired.

Schema of Trial: Results of F-18 FDG PET visual interpretation were compared to biopsy or cytology results. The PET results were also compared to CT results.

Image Protocol: Image acquisition and reconstruction was stated in the study, however, attenuation correction was not mentioned.

Two radiologists reviewed the images immediately after completion of each study to determine technical image quality. Qualitative assessment was performed while reading from the monitors. The images were manipulated and displayed and processed into transverse, coronal, sagittal, and normalized whole-body projection and volume views. PET

scans were compared to CT images in a non-masked manner. Interpretations were rendered.

Primary Endpoints: Visual interpretation of F-18 FDG PET studies, CT results, and histology or cytology.

Results: AJCC stages of the patients were: 28 stage II, 28 stage III, and 20 stage IV.

Of the 103 scans, 100 were evaluable. The sensitivity of PET scanning for the detection of melanoma metastases was 49 of 52 cases (94%) and specificity was 40 of 48 cases (83%).

CT scans were considered false negative if they failed to identify all lesions detected by PET scanning. Because not all PET identified lesions were biopsied, CT results were not considered by this medical reviewer

A table summarizing PET and CT scan results relative to biopsy results, sites of positive tests was presented.

Safety Issues: The study stated each lot of F-18 FDG was analyzed to confirm radionuclide, radiochemical, and chemical purity as well as sterility and pyrogenicity.

Commentary: This study's endpoint of comparing PET to CT was not appropriate because it used F-18 FDG PET results as a standard of truth. Therefore, this review only considered the results of F-18 FDG PET and histology. The study only presented results by scan and not by patient. F-18 FDG PET scans were read with CT scans, which may have biased PET readings. There is no mention of how the two readers decided on a single interpretation and there was no accounting of inter- and intra-reader variability. As with Friess (1995), intravenous furosemide was used, but no data is presented on this drug's affect on F-18 FDG imaging despite the drug's known affects on glycolysis and serum glucose levels.

Lowe VJ, Hoffman JM, DeLong DM, Patz Jr. EF, Coleman RE. Semiquantitative and visual analysis of FDG-PET images in pulmonary abnormalities. J Nucl Med 1994;35:1771-1776.

This study of 88 patients from the St. Louis University Medical Center, Missouri prospectively analyzed F-18 FDG PET images in patients with pulmonary abnormalities to evaluate use of SUV or qualitative visual interpretation. The study concluded that SUV and visual interpretation were both accurate methods of F-18 FDG PET data analysis in differentiating malignant from benign focal pulmonary abnormalities.

Inclusion Criteria: Between November 1991 and March 1993, 107 patients found to have radiologically indeterminant focal pulmonary abnormalities were referred to F-18 FDG PET imaging. Ninety-three patients had a definitive diagnosis made by histology, but 5 patients were excluded from the analyses because their PET data was not retrievable or there were technical problems related to patient positioning. Four patients had type II diabetes.

Dose: After fasting at least 4 hours, 10 mCi of F-18 FDG was injected intravenously and emission images were obtained 30 minutes after injection.

Schema of Trial: Comparison of SUV versus visual interpretation of F-18 FDG PET scans for pulmonary lesions using receiver operating characteristic curve analysis.

Image Protocol: Transmission scans were performed on all patients either prior to injection of F-18 FDG or prior to emission image acquisition. Acquisition and reconstruction were described. A nuclear medicine physician and a chest radiologist used CT and chest radiographs to locate abnormalities on F-18 FDG PET images. The physicians were masked to biopsy results. Regions of interest were placed over the most intense area of F-18 FDG activity (2.7 ± 1.4 cm2). After correction for radioactive decay, the regions of interests were analyzed by computing SUVs. No partial volume correction was applied.

Two nuclear medicine physicians masked to biopsy results and anatomical data were shown transmission and emission scans. They visually compared transmission and emission image abnormalities. They individually graded the images depending on their confidence of malignancy based on their knowledge of normal F-18 FDG update within the thorax on a five-point scale with 5= definitely tumor, 4= probably tumor, 3=equivocal, 2=probably not tumor, and 1= definitely not tumor. They also graded lesions compared to mediastinum uptake on a five-point scale with 5>> mediastinum, 4> mediastinum, 3= mediastinum, 2< mediastinum, and 1<< mediastinum. Anatomical information from chest x-ray and CT was given to the nuclear medicine physicians who then individually regraded the PET studies. On review, if the two readers did not concur on their grading of the lesion, the readers discussed their differences and reached a consensus interpretation. Receiver operating characteristic curves were then generated for the different techniques of evaluation using a nonparametric approach.

Primary Endpoints: SUV in abnormal regions of interest and normal regions of the lung were calculated. SUV of >2.5 was considered positive. Visual interpretation graded on a 5-point scale was obtained (4 or 5 considered positive for malignancy). F-18 FDG uptake in the abnormality was also visually graded in comparison to mediastinal activity. Biopsy information was obtained for a definitive diagnosis. Receiver operating characteristic curves were generated.

Results: Of the 88 patients with biopsy information, 61 had malignancy and 27 patients had a benign finding. Seventy-eight of the 88 patients had well-defined abnormalities on conventional imaging with 72 of the 78 being pulmonary nodules of $\leq$4 cm. Diagnoses were made by bronchoscopy, transthoracic thin-needle aspiration, thoracotomy, or, in one patient, radiographic stability for over 8 years.

The area under the receiver operating curve characteristic for SUV was 0.96 (95% confidence interval 0.91 to 1.0) and for visual analysis by consensus reading was 0.96 (95% confidence interval 0.90 to 1.0). Both readers had performance of visual interpretation tracked and comparison revealed excellent agreement. Tracking was also done on reader performance with and without anatomic information provided at the time of F-18 FDG PET interpretation. Results of the performance were presented in a table and revealed no difference of performance when using or not using chest x-rays and CT scans for localization of abnormalities for each reader.

Of the four patients who had diabetes (all type II), all were correctly identified by SUV and visual interpretation.

Safety Issues: The study mentions F-18 FDG was tested for sterility, pyrogenicity, and radiochemical purity on each production run. No other safety issues were mentioned.

Commentary: This study provided information on visual interpretation and SUV accuracy. Of note, the authors studied use of visual information with and without anatomical data to assist in locating abnormalities found on conventional imaging. Because many studied used conventional imaging to locate lesions, this has been raised as a possible mechanism that would bias readers. This study presented detailed information on the affect of anatomical information for each reader's interpretation of the probability of tumor and on F-18 FDG activity relative to mediastinum activity on the area of the receiver operator characteristic curve. The affect appears to have been minimal for the study's readers.

One consistent weakness reflected in this study and others is that a significant SUV to define malignancy was derived retrospectively rather than tested as a hypothesis.

Moog F, Bangerter M, Kotzerke J, Guhlmann A, Frickhofen N, Reske SN. 18-F-fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. J Clin Oncol 1998;16:603-9.

Bone marrow biopsy of the iliac crests is the standard for diagnosing bone marrow involvement with malignant lymphoma. However, its sensitivity is less than optimal. This study of 78 patients from the University of Ulm, Germany, investigated the efficacy of F-18 FDG PET as a new method to evaluate bone marrow involvement in patients with malignant lymphoma.

Inclusion Criteria: Between July 1992 and October 1996, 78 consecutive patients with biopsy-proven and untreated lymphoma were prospectively enrolled into the study. Thirty-nine patients had Hodgkin's lymphoma, 10 patients had nodular sclerosis, 18 had mixed celluarity, and 3 had lymphocyctic predominance. The remaining 39 patients had non Hodgkin's lymphoma. The 42 women and 36 men ranged in age from 7 to 73 years. All patients were examined with F-18 FDG PET and bone marrow biopsy (70 bilateral and 8 unilateral) within 3 weeks (median 8 days) before therapy.

Dose: Patients fasted for at least 8 hours before the examination. A mean dose of 270 MBq (range, 250 to 350 MBq) was injected intravenously. Static emission scans were taken 50 to 60 minutes after injection.

Schema of Trial: Comparison of visual analysis of F-18 FDG PET images and iliac crest biopsies.

Image Protocol: Acquisition and reconstruction were stated in the study. Attenuation correction was performed. Patients were repositioned using laser-guided landmarks for emission and transmission scans. Evaluation of PET images was performed by masked and independent visual interpretation by two board-certified nuclear medicine physicians. Transaxial, coronal, and sagittal sections were reviewed on film. In individual cases, additional evaluation on the monitor was performed with alteration of the gray scale. Any foci with significant increase in F-18 FDG uptake in comparison with the surrounding bone marrow were considered suspect for lymphoma. These visual findings were graded on

a three-point scale as "mild," "moderate," or "marked." Malignancy was defined as all "marked" cases and "moderate" cases with increased size, asymmetry, and irregular shape. Quantitative analysis of F-18 FDG uptake was not performed. The final diagnosis was determined by consensus of both observers. Bone marrow biopsies and F-18 FDG PET images were evaluated masked to each other.

To clarify the 10 negative biopsy/positive F-18 FDG PET findings, four patients underwent a second biopsy, one patient underwent a polyermase chain reaction, and two cases underwent MRI, and 3 cases did not undergo dispute resolution or further work up.

Primary Endpoints: Primary endpoints were diagnosis on iliac crest biopsies and PET visual interpretations.

Results: There were 78 patients who had F-18 FDG PET finding compared with bone marrow biopsy. Seven of eleven patients who had a positive bone marrow biopsy had a positive F-18 FDG PET scan giving a sensitivity of 64%. Fifty-seven of sixty-seven patients who had negative biopsies had negative F-18 FDG PET scans giving a specificity of 85%. The study goes on to present data on the 10 patients who had a negative bone marrow biopsy but positive PET scan. These discordant test results underwent further testing or clinical examination to reveal 8 of the 10 having marrow involvement.

Patient information is presented for all F-18 FDG PET positive and biopsy positive patients.

Safety Issues: No safety issues were reported in the study.

Commentary: This study, similar to Carr (1998), presented combined results of both Hodgkin's lymphoma and non-Hodgkin's lymphoma, which may not be appropriate. The authors note that untreated non-Hodgkin's lymphoma may have bone marrow involvement in roughly 19 to 83% of patients. For Hodgkin's lymphoma, the estimates are from 5 to 14%. These differing estimates suggest the disease entities with respect to bone marrow involvement may be different. This study also used discrepancy resolution of only the PET positive, bone marrow biopsy negative cases. This is a biased approach to resolving discordant cases favoring the new technology. It also assumes that no errors in classification are made with respect to the other cells of the 2x2 table (PET negative, biopsy negative; PET positive, biopsy positive; and PET negative, biopsy positive).

Sazon DA, Santiago SM, Soo Hoo GW, Khonsary A, Drown C, Mandelkern M, Blahd W, and Williams AJ. Fluorodeoxyglucose-positron emission tomography in the detection and staging of lung cancer. Am J Respir Crit Care Med. 1996;153:417-21.

This study is from the Veteran's Administration Medical Center West Los Angeles, California. Sensitivity and specificity of F-18 FDG PET imaging for the diagnosis and staging of lung cancer in 107 patients with an abnormal chest x-ray was determined based on pathological diagnosis established by a variety of means. Chest CT scans were also performed and these results were compared to F-18 FDG PET results.

Inclusion Criteria: One hundred and seven patients who were being evaluated for abnormal chest x-rays between August 1992 and March 1994 were studied with whole-body F-18 FDG PET imaging. All patients except for one were men (mean age 62 ±9 years of age). Radiographic abnormalities ranged from interstitial infiltrates to masses.

Dose: IV administration of 10 mCi F-18 FDG; patients imaged in the fasting state (the duration of fasting is not stated) 40 minutes after injection.

Schema of Trial: A comparison of results from F-18 FDG PET with pathology. Chest CT scan of the mediastinum was performed in those patients needing mediastinal evaluation and these results were compared to F-18 FDG PET and pathology.

Image Protocol: PET scan results were interpreted by nuclear medicine physicians who were masked to the patient's diagnosis. Chest CT was performed from supraclavicular region to the adrenal glands to assess mediastinal nodes in a subset of patients needing mediastinal evaluation. CT results were interpreted by staff radiologists masked to the patient's diagnosis. The CT studies were interpreted independently from the PET studies. The article mentions how PET images were obtained and reconstructed but attenuation correction was not mentioned. There was no mention how many physicians read each image and if inter- or intra-variability of interpretations was tracked. The PET and CT scans were performed in close temporal proximity as part of the immediate evaluation of the patient.

Primary Endpoints: PET Scan results were interpreted qualitatively as either positive or negative based on the presence or absence of any increased F-18 FDG uptake in the lungs and/or mediastinum. Chest CT were interpreted as

either positive or negative based on the presence or absence of mediastinal node enlargement defined as node > 1 cm in diameter on transaxial images. Pathologic diagnosis was established by sputum examination, bronchoscopy, percutaneous fine needle aspiration biopsy, or thoracotomy. Mediastinal nodal evaluation was accomplished by transbronchial needle aspiration biopsy, mediastinoscopy, thoracotomy, or autopsy. Absence of mediastinal nodal metastasis was reported only if confirmed at thoracotomy or autopsy.

Results: One hundred seven patients with abnormal chest x-rays underwent evaluation with PET and pathological diagnoses were obtained in all of them. Eighty-two patients had lung cancer, and 25 patients had non-malignant diseases of the chest. Of the 82 patients with malignancy, 73 patients had non-small cell cancer (33 squamous cell, 28 adenocarcinoma, 12 undifferentiated), five had small cell cancer, and four had lung metastasis. Mediastinal evaluation was performed in 32 patients with non-small cell carcinoma. The rest of the patients were assessed to be nonsurgical candidates by other criteria, and confirmation of nodal involvement was not pursued. Of the 32 patients who had mediastinal evaluation, 22 underwent thoracotomy, two had mediastinoscopy, four by transbronchial biopsy, four by autopsy), 16 were found to have nodal metastasis. PET scans were positive in all sixteen cases that were found to have metastasis on tissue confirmation. Sixteen PET scans were negative for those 16 patients who did not have a tissue diagnosis of mediastinal involvement. CT scans were positive in 13/16 patients with confirmed mediastinal tissue diagnosis of cancer; 9/16 CT scans were negative in patients without mediastinal tissue diagnosis of cancer.

The results for F-18 FDG PET in this study show a sensitivity of 100% and a specificity of 52% in patients with an abnormal chest x-ray.

The study also published all pathology findings of non-malignant cases. There were 25 non-malignant cases: 10 cases of sarcoidosis, 4 coccidiodomycosis, 3 mycobateria, and 8 others. For the 12 F-18 FDG PET scans that were false positive, the study reports 4 were cases of sarcoidosis, 3 of coccidiodal pneumonia, 3 of mycobacteria, and 2 others. Of note, the study does describe differences between the observed pattern for true positive scans and false positive scans. For lung cancer, the pattern of uptake was focal and discrete; for patients with false positive PET scans, the pattern was consistently less intense and more diffuse.

Safety Issues: The study did not mention any adverse events associated with F-18 FDG administration.

Commentary: The study encompassed the proper study population for F-18 FDG PET oncology imaging: those who have an existing chest x-ray abnormalities undergoing further evaluation. There are pathology results for all patients. Absence of mediastinal nodal metastasis was reported only if confirmed at thoracotomy or autopsy. The broad spectrum of disease ranging from different types of lung cancers and metastasis to benign inflammatory processes was included in the study. Image acquisition and reconstruction was documented in the study. Readers were masked to the clinical diagnoses of the patients. PET and CT images were read separately by nuclear medicine physicians and staff radiologists respectively.

Deficiencies of the study include the absence of intra-reader and inter-reader variability and the absence of CT scan results except in patients with mediastinal nodal evaluation.

Schiepers C, Penninckx R, De Vadder N, Merckx E, Mortelmans L, Bormans G, Marchal G, Filez L, Aerts R. Contribution of PET in the diagnosis of recurrent colorectal cancer: comparison with conventional imaging. Euro J of Surgical Oncology 1995;21:517-522.

This study from the University Hospital Gasthuisberg, Belgium investigated total body F-18 FDG PET in 76 patients presenting with or suspected of recurrent local or distant colorectal cancer. PET results were compared to routine imaging (CT pelvis, CT/ultrasound of liver, and chest x-ray).

Inclusion Criteria: From May 1990 through June 1993, 76 consecutive patients were referred for work up of suspected recurrent colorectal cancer. There were 45 men and 31 women, mean age was 59 years. They had been followed at 6-month intervals with clinical examination, proctoscopy, serum CEA, ultrasound of the liver and chest x-ray. Routine colonscopy was performed 1 year after surgery.

Dose: A dose of 400-550 MBq F-18 FDG was administered intravenously. Imaging began 50 minutes later. Patients were studied in the fasting state (> 6 hours). The bladder was continuously flushed via a triple lumen catheter

Schema of Trial: In total, 83 studies were performed in 76 patients. PET results were compared to a final diagnosis

obtained in 52 studies with surgery or biopsy, and in 31 studies with clinical follow up for at least 14 months. A subgroup of 74 studies had CT-pelvis and another subgroup of 80 studies had CT and/or ultrasound of the liver to compare with PET images.

Image Protocol: The images were not corrected for tissue attenuation. Acquisition is described in the study. Masking was not stated.

Primary Endpoint: Pathology results from biopsy or surgery, or clinical follow up for at least 14 months.

Results: The mean interval between PET and surgery/biopsy was 42.5 days (median 24). For 31 studies, the final diagnosis was established with clinical follow of at least 14 months. For recurrence in liver and pelvis, total body PET had a sensitivity of 94% (45/48) and a specificity was 97% (34/35).

For local recurrent disease in the pelvis, 74 studies had a PET and CT-pelvis within 2.5 months. Final diagnosis for 27 of 74 studies was derived from clinical follow up of at least 14 months and the remaining 47 studies had surgical or biopsy diagnoses. PET had a sensitivity of 93% (42/45) and specificity of 95% (28/29). CT had a sensitivity of 60% (27/45) and specificity of 72% (21/29). Results according to clinical follow up and surgery/biopsy are also presented.

For metastatic disease to the liver, 73 patients had 80 studies with PET and liver examination with CT and/or ultrasound within 2.5 months. Final diagnosis for 28 studies was obtained from clinical follow up of at least 14 months and the remaining 52 studies had surgery or biopsy. PET sensitivity was 94% (32/34) and specificity was 100% (46/46). CT and/or ultrasound had a sensitivity of 85% (29/34) and specificity of 98% (45/46). Results according to clinical follow up and surgery/biopsy are also presented.

Distant lesions discovered with total body PET are presented. PET detailed 25 unexpected lesion locations in 20 patients; 14 lesions (56%) were confirmed with pathology results or directed radiography or CT. All false-positive readings occurred in the thorax, 10 in the lungs and 1 in the axilla. Absence of disease was confirmed with long term clinical follow up. There was also one false negative, an ovarian cancer metastasis discovered during laparotomy, which was not seen on the PET study 6 months earlier.

Safety Issues: No adverse events were mentioned with F-18 FDG administration.

Commentary: The study population was appropriate. There were 45 patients with malignant recurrence and 29 patients with benign conditions. The standard of truth in this study varied from use of pathology to other imaging modalities that are routine in cancer follow up to long term clinical observation. While validation of tumor in liver and distant sites depended in part on imaging, there was also long term follow up of at least 14 months to address possible false-negatives.

The image protocol was not well described. In particular, the study did not mention masking nor who read the images with what criteria. There is no mention of reader variability. CT results were only available for mediastinal work ups.

Utech C, Young CS, Winter PF. Prospective evaluation of fluorine-18 fluorodeoxyglucose positron emission tomography in breast cancer for staging of the axilla related to surgery and immunocytochemistry. Eur J Nucl Med 1996;23:1588-93.

This study is from the University of Illinois College of Medicine and Downstate Clinical PET Center at the Methodist Medical Center of Illinois. This study investigated noninvasive staging of axillary lymph nodes for metastases in 124 patients with a diagnosis of breast cancer prior to surgery by F-18 FDG PET.

Inclusion Criteria: Prior to any therapeutic intervention, 124 patients with newly diagnosed and histologically proven breast carcinoma were studied by F-18 FDG PET. The average age of the patients was 59 years (range 32-94 years). Clinical staging revealed lymph nodes in then patients, while mammography reports mentioned axillary lymph nodes in four patients.

Dose: Patients fasted for 4 hours prior to the study, with the majority of patients undergoing an overnight fast. Transmission scans were performed and then 10 mCi of F-18 FDG was injected intravenously through a previously placed catheter on the side contralateral to the primary breast tumor (except in one patient). Sixty minutes after injection the emission scan was acquired.

Schema of Trial: Comparison of lymph node metastasis status with F-18 FDG PET readings. Other immunocytochemistry

parameters were also measured to assess correspondence with PET scan.

Image Protocol: Acquisition and reconstruction was discussed. Images were corrected for randoms, detector efficiency, photon attenuation, dead time, and radioactive decay. Differential uptake ratios (DUR)were calculated for axillary nodal uptake. A cutoff point of DUR values of 1-3 for metastases and 3 and higher for tumor.

The images were initially reviewed by three experienced nuclear radiologists and the final reading for the study was made by an experienced nuclear medicine physician from films and a video monitor using gray-scale display. The reader was masked to the patients lymph nodes status, but the reader did know the diagnosis of breast cancer. A scan was read as positive if a discrete focal uptake greater than background was identified. Otherwise, scans were read as negative.

The diagnosis of cancer was made by core biopsy in 52 patients, by excisional lumpectomy in 67, and by wide excision in five.

Of the 124 patients, 68 underwent modified radical mastectomy, 28 partial mastectomy and lymph node dissection, ten lumpectomy and lymph node dissection, and seven re-excision and lymph node dissection after biopsy. One patient had a bilateral modified radical mastectomy. Ten patients did not undergo additional surgery after biopsy since the tumor was completely excised, but underwent separate nodal dissection. The anatomic levels of axillary lymph nodes were determined by their position relative to the musculature markings. The written pathology report was the basis for evaluating the number and extent of involved lymph nodes.

Primary Endpoints: F-18 FDG PET scan interpretation of axillary nodes and pathology findings. Differential uptake ratios were calculated and correlated with size, grade, S-phase, receptor status, and ploidy.

Results: PET correctly identified all 44 tumor-positive axillary lymph nodes for a sensitivity of 100%. Sixty tumor-negative axillary nodes were negative by PET and 20 tumor-negative nodes were positive by PET giving a specificity of 75%. A weak correlation was found between the differential uptake ratio and tumor size and S-phase of the tumor. Clinical follow up for 1-2 years showed no recurrence of the disease in patients identified as false-positive by pathology.

Average number of nodes dissected for the true-positives was 20 (range 7-39), 16 (range 7-36) for the true-negatives, and 20 (range 9-46) for the false positive.

Detailed tables with patient results are presented.

Safety Issues: No safety issues were mentioned in the study.

Commentary: This study does not provide information on selection criteria, interpretative criteria, and why the protocol called for 2 readers than another reader making a definitive reading. There is no statement on whether the diagnosis, known to the reader, included laterality of cancer. There is a possibility that initial diagnostic surgery may have interfered with the F-18 FDG PET scanning. However, the study reports only two of the twenty false positives as having reactive nodes on pathology. The study also notes that there were differences in level of node dissection, with some patients having nodes dissected to Level I and others to Level III.

Valk PE, Pounds TR, Hopkins DM, Haseman MK, Hofer GA, Greiss HB, Myers RW, Lutrin CL. Staging Non-small cell lung cancer by whole-body positron emission tomographic imaging. Ann Thorac Surg 1995;60:1573-82.

This study is a prospective evaluation of regional and whole-body PET imaging for staging lung cancer carried out by the Northern California PET Imaging Center, California in 99 patients.

Inclusion Criteria: All patients who were referred to the Northern California PET Imaging Center for staging of histologically diagnosed non-small cell lung cancer from October 1992 to January 1995 were included. Also included were patients who were initially imaged for diagnosis of indeterminant pulmonary nodules and who proved to have non-small cell lung cancer on subsequent histologic diagnosis. Ninety-nine patients were enrolled in the study, including 53 men and 46 women, ranging from age from 46 to 87 years (mean, 66 years). Sixty-seven patients were referred for staging of known lung cancer and 32 were referred for diagnosis of lung nodules.

Dose: Patients fasted for at least 4 hours before intravenous injection of 0.143 mCi/kg of F-18 FDG, for an average dose of 10 mCi. Whole-body imaging were acquired 30 minutes after injection.

Schema of Trial: An evaluation of regional and whole-body PET imaging for staging of lung cancer. Mediastinal PET and CT results were compared with surgical staging and clinical and imaging follow up.

Image Protocol: Acquisition, image reconstruction, and display were mentioned in the study. Whole body images were not corrected for attenuation. First whole-body imaging was performed and then two static 20-minute emission acquisitions were performed with the imaging volume centered first on the mediastinum and then on the liver. Transmission imaging was performed in the first 42 patients before injection and in the remaining patients it was performed after emission scans. All PET images were interpreted at the time of the study by one or two nuclear medicine physicians. Images were viewed in axial, coronal, and sagittal planes using an interactive video display system. When CT images of the chest were available, these were used for localization and measurement of the primary tumor and other pulmonary opacities. Mediastinal CT findings were disregarded. No other images were available at the time of interpretation. Overlays of emission and transmission PET images were used to localize metabolically active peripheral lung lesions in some cases. PET images of the chest and abdomen and whole-body were read as positive or negative for metastatic tumor.

SUV were determined for primary lesions that were 2 cm or more in diameter.

All mediastinal images were reread at the conclusion of the study by two authors to evaluate the effect of increase in experience in PET interpretation during the study. Images were reread independently by the two investigators without knowledge of patient information or histologic data. Readings were subsequently compared, and consensus was reached by discussion. At rereading, mediastinal images were graded on a 3 point visual scale: 0=activity less than or equal to the mediastinal blood pool activity; 1+= activity slightly but definitely above the mediastinal blood pool activity; 2+= activity markedly above the mediastinal blood pool activity. A score of 1+ or 2+ was considered positive for malignancy.

CT scans were performed before the PET study in all cases in one of 6 imaging centers. Sixty-two studies were performed after intravenous injection of 100 to 200 cc of contrast material. Fifty-two of the 99 patients had also undergone contrast-enhanced CT imaging of the abdomen and pelvis. All chest CT scans were reinterpreted for mediastinal staging by

two authors. Lymph node measurements of greater than 1 cm were considered positive for metastasis. Each study was read as positive or negative for mediastinal metastasis. Readers were masked to the clinical data, PET findings, and histologic diagnosis.

Primary Endpoints: Tissue for histologic diagnosis was obtained at thoracotomy or mediastinoscopy. The side of the mediastinum that was explored was assessed as involved or uninvolved according to the histologic diagnosis obtained from sections of lymph node specimens. Midline nodes were considered ipsilateral to the primary lesion. In ten patients with CT abnormalities, absence of clinical disease 6 to 28 months after imaging was accepted as evidence against metastasis. Sensitivity, specificity, mean values of SUVs of lesions were determined.

Results: Ninety-nine patients with 102 primary lung cancers were studied. The histologic tumor types included adenocarcinoma (43 cases), squamous cell carcinoma (35), large cell carcinoma (8), undifferentiated carcinoma (17) and unspecified non-small cell (5), bronchoalveolar (2), and adenosquamous (2). No validation of mediastinal findings was obtained in 25 patients and their studies were excluded from analysis.

N2 nodal stage was demonstrated in 24 patients of 76. PET study was positive in 20 of 24 cases (83%) for mediastinal metastasis and negative for 49 of 53 cases without mediastinal metastasis (94%). CT had a sensitivity of 15 of 24 cases (63%) and specificity of 38 of 52 cases (73%).

Eleven patients had evidence of unsuspected distant metastatic disease on PET with eight of these eleven having confirmation on biopsy (2 cases) or clinical progression of the disease on other scans (bone scans or CT scans (5 cases), or death, 1), with three cases without any follow up data. Normal PET findings were obtained at distant sites of computed tomography abnormality in 19 patients. Fourteen of these 19 had histologic confirmation (1 case) or clinical confirmation (14 cases) that the PET diagnosis was correct. In one lung lesion, the PET result proved to be falsely negative at a 5 month follow up CT scan. The remaining 4 cases did not have follow up data. The minimum follow up time for 13 cases was a mean of 12 months (range 6 months to 26 months).

The mean SUV was 9.6 $\pm$3.7 (range 3.2 to 22.3) for 68 histologically confirmed malignancies.

Safety Issues: No safety issues were mentioned in the study.

Commentary: This study provides data on F-18 FDG PET imaging detection performance in evaluating mediastinal nodal status and distant metastasis. The study was not a controlled trial of F-18 FDG PET versus CT scan. CT scan results were used in PET evaluation to identify locations of some abnormalities. PET scans were initially read and then they were reread retrospectively with readers masked to histology and other imaging. SUV were analyzed retrospectively. Resolving discrepancies between F-18 FDG PET and CT are difficult, but the authors made attempts either to biopsy lesions or have the patients followed. Despite this, 3 of 11 PET positive/ CT negative for distant metastasis and 4/19 PET negative/CT positive cases for distant metastasis did not have follow up data.

Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Bogaert J,, Maes A, Deneffe GJ, Nackaerts KL, Verschakelen JA, Lerut TE, Mortelmans LA, Demedts MG. Lymph node staging in non-small cell lung cancer with FDG-PET scan: a prospective study of 690 lymph node stations from 68 patients. J Clin Oncol 1998;16:2142-2149.

This study of 68 patients from the University Hospital Gasthuisberg, Belgium compares the accuracy of CT scan and F-18 FDG PET visually correlated with PET plus CT in the local and regional lymph node staging of non-small cell lung cancer.

Inclusion Criteria: Eligible patients had suspected or biopsy-proven non-small cell lung cancer. Standard staging for distant metastases was negative. Exclusion criteria were a fasting blood glucose level greater than normal (5.8 mmole/L), diabetes mellitus, treatment with corticosteriods more than 0.125 mg/kg of prednisone, congestive cardiomyopathy preventing lying down flat for scans, direct mediastinal invasion by the primary tumor, and obvious bulky mediastinal adenopathies, schedule limitations of the imaging or surgery department. Sixty-eight patients were studied between September 1995 and January 1997. Their mean age was 64 years (range, 40 to 83 years).

Dose: Patients fasted for at least 6 hours before being injected intravenously with 6.5 MBq/kg of F-18 FDG into the opposite arm of the tumor. A 60-minute dynamic emission study of the upper half of the thorax was started at the time of injection, followed by a 10-minute static acquisition.

Schema of Trial: CT, F-18 FDG PET and invasive surgical staging were performed in one month of each other. Sensitivity and specificity of CT and CT with PET was calculated. SUR and ROC analysis for metastasis of lymph nodes were also studied.

Image Protocol: All data were corrected for decay and photon attenuation. Acquisition and reconstruction information was provided in the study. Transaxial, sagittal, and coronal images were used for interpretation by reading on the image display. This was performed prospectively and masked to surgical pathological data by two readers from nuclear medicine and one chest physician. A five-point scale was used for the interpretation of lymph nodes: 1= not visible on the image display; 2= lower intensity than mediastinal blood pool activity; 3= equal to mediastinal blood pool activity; 4= more intense than mediastinal blood pool activity; and 5= much greater intensity than mediastinal blood pool activity. A lymph node was considered to be metastatic when the F-18 FDG-uptake was classified as grade 4 or 5. Grades 1 through 3 were considered benign. Localization of lymph node uptake zones on PET was performed by a projection of the hot spots on the reconstructed transmission images on which the trachea and main bronchi are more visible, and by visual comparison of PET and CT. Abnormal uptake of nodes was recorded on a nodal map. PET findings determined nature of the lymph nodes and CT determined localization for analyses.

CT was performed from adrenals to supraclavicular regions. A power injector was used to perform a bolus injection of 2 cc per second of contrast medium during 40 seconds. Lymph nodes 1.5 cm or greater at their maximum cross-sectional diameter were considered to be metastatic. All examinations were prospectively interpreted by a chest radiologist and a chest physician unaware of the surgical pathology results. The nodal stage determined by CT and the suspect lymph node stations were noted on a map.

Primary Endpoints: PET interpretations, CT interpretation, and histology were primary endpoints. SUV of lymph nodes using regions of interests drawn manually on transaxial images around focal uptake areas provided information for a retrospective analysis to determine the relationship between the SUVs of the lymph nodes and diagnosis through ROC analysis. Invasive surgical staging is described in detail, midline nodes were considered ipsilateral.

Results: Sixty-eight patients had final pathologic nodal staging of: N0 in 34 patients, N1 in six patients, N2 in 24

patients, and N3 in four patients. Histology was available for 690 nodal stations based on 45 patients undergoing surgery, 22 patients undergoing mediastinal exploration only, and 1 patient had a fine-needle biopsy of a supraclavicular node only.

CT correctly identified the nodal stage of 40 of 68 patients (59%). Understaging occurred in 12 patients and overstaging in 16 patients. PET plus CT was accurate in 59 of 68 patients (87%). Understaging occurred in 5 patients and overstaging in four patients.

In the detection of locally advanced disease (N2/N3), the sensitivity and specificity were 75% (21/28) and 63% (25/40) for CT. For PET plus CT, this was 93% (26/28) and 95% (38/40) respectively. In the receiver operator characteristic curve, the best SUV threshold to distinguish benign from malignant lymph nodes was 4.40. The analysis with SUV threshold was not superior to the use of a five-point visual scale.

Safety Issues: No safety issues were mentioned in this study.

Commentary: This study compared the addition of F-18 FDG PET to CT in diagnosing local and regional lymph node metastasis for non-small cell cancer of the lung. In the study, use of CT scan for localization did not bias interpreters as this was accounted for in the hypothesis. However, in a true factorial design to assess contribution of each modality, PET imaging alone should have been done. Histology data is present for all patients. All tests and histology were obtained within one month of the each other. Inter- and intra-reader variability , how images were read between the two or three readers, and how a diagnosis was derived were not mentioned.

C. Discussion of Effectiveness

The efficacy data supporting the indication for F-18 FDG PET imaging for the determination of abnormal glucose metabolism to assist in the evaluation of malignancy is derived from the published medical literature. As outlined in FDA's guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998), FDA can, in certain circumstances, rely on published reports alone to support approval of a new product. FDA has outlined factors that increase the possibility of reliance on published reports alone to support approval of a new product. These include: 1) multiple studies conducted by

different investigators where each of the studies clearly has an adequate design and where findings across studies are consistent; 2) a high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), study endpoints, and a full accounting of all enrolled patients; 3) clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment; 4) robust results that yield a consistent conclusion of efficacy and do not require selected post hoc analyses; 5) conduct of studies by groups with properly documented operating procedures. As a body of literature taken together, the 16 reviewed studies, including two adequate and well-controlled studies (Lowe (1998) and Carr(1998)), provide the cumulative evidence to support effectiveness of F-18 FDG PET for the determination of abnormal glucose metabolism to assist in the evaluation of malignancy in humans. See Table 1.

The 16 studies encompassed a variety of cancers: non-small cell lung cancer, colo-rectal, pancreatic, breast, thyroid, melanoma, Hodgkin's disease, non-Hodgkin's lymphoma, and other metastatic cancers to lung, liver, bone, and axillary nodes. There were 1,311 patients from all the studies combined. The majority of studies were conducted with patients who were fasting for at least 4 hours (range, at least 4 to at least 12 hours) prior to intravenous injection of F-18 FDG. The dose used was between 200 MBq to 740 MBq F-18 FDG (mean dose, 376 MBq). Two studies provided dosing information based on patient weight: Valk (1995) used 5.3 MBq/kg (0.143 mCi/kg) and Vansteenkiste (1998) used 6.5 MBq/kg. Only one study, Holder (1998), utilized a dose over 550 MBq. The averaged dose of 370 MBq presently has pharmacologic/toxicologic data from a previously approved new drug application of F-18 FDG to support that dose's safety and would be acceptable for labeling purposes for this review's indication. A range of doses could be provided in the clinical studies labeling section. After intravenous administration of F-18 FDG, static emission scans were acquired after at least 30 minutes from the time of injection (range, 30 to 101 minutes; mean, 53 minutes).

F-18 FDG was approved in 1994 for PET imaging for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures. The approved labeling recommends a dose for adults within the range of 185 to 370 MBq (specific activity of no less than 1.9×10^4 Ci/mmol in 16 mL of isotonic saline). This review of the PET oncology literature finds a maximum dose about twice the maximum previously approved dose.

This review included studies of various malignancies that met the inclusion criteria. For some malignancies, such as melanoma, pancreatic and thyroid cancer, there was only one article reviewed, while for other cancers such as lung and breast cancer, more articles were reviewed. It must be remembered that many other articles exist about F-18 FDG performance in these cancers, but they did not meet this review's inclusion criteria. While it is recognized that cancer is not one single disease process, most cancerous cells do share increased rates of glucose metabolism, which is the basis for F-18 FDG PET imaging. This differential in glucose metabolism compared to normal or benign tissue is the basis for F-18 FDG PET effectiveness to assist in the evaluation of malignancy for patients with abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer. However, as shown in the studies, the performance of F-18 FDG PET differs from study to study, from among same tumor types, and across different tumor types. For example, there is suggestion that low-grade non-Hodgkin's lymphoma and bronchioalveolar carcinoma may not have increased F-18 FDG uptake. Moreover, there were benign conditions that also demonstrated similar patterns of increased glucose metabolism. Despite this variability, there still are acceptable levels of performance and clinical benefit to permit generalization of use to evaluate malignancy.

There are, however, limitations with using published literature in evaluating safety and effectiveness. Publication bias may be reflected in that positive studies of the new technology are more likely to be published than negative findings. The inclusion criteria used in this review of English language articles and publications found in electronic data bases may have also introduced bias. In addition, surgery and clinical oncology journals may not wish to devote space to publishing detailed methodology for image acquisition, imaging interpretation procedures, and image interpretation criteria. Many details about image evaluation were absent from the studies. Inter- and intra-reader variations in interpretation were, on the whole, either not mentioned, or discussed in limited fashion. For example, only three studies, Avril (1996), Lowe (1998), and Carr (1998), presented correlation coefficients for readers. However, Avril (1996) correlated readers' circling regions of interest for SUV analysis and not qualitative interpretation. Lowe (1998) and Carr (1998) presented information on reader agreement using the kappa statistic and explanation of how many cases and how disagreements were resolved. One study (Lowe, 1994) did present ROC information

on image interpretation for both readers with and without anatomical (CT) information, providing area under the curve, standard deviation and 95% confidence intervals. Although there is some experience in the medical community with F-18 FDG PET imaging in oncology, variations of interpretation can still be expected given the subjective nature of the image interpretation process, the varying capabilities of the physical imaging detection systems, and the still growing understanding of the field. Therefore, mechanisms to assess and control interpretation variation should be part of imaging protocols. However, should F-18 FDG PET quantitative analysis develop into an accurate, precise, and standardized methodology across different PET facilities, this would decrease concerns about subjective interpretation although the other causes of variability would have to be addressed. Finally, in the imaging community there has been debate on whether kappa statistic is appropriate. This statistic corrects for agreement, in this case imaging interpretation agreement, due to chance. This implies a model in which there are ranges of image features or stimulus strength for which the reader is guessing (leaving to chance) about the presence or absence of disease. This model belongs to a family of so-called "threshold models." However, these models are inconsistent with the form of ROC curves measured in diagnostic imaging. Readers are not guessing about the presence of a signal or disease, but are able to report on the strength of the image features as they perceive them. This is done through confidence-ratings (on a point system of 1-100 with 100 being 100% confidence that disease is present) or probability scales (also from 1-100%). It is the range of reading skills and the inability of image readers to maintain, or remember, a constant mindset (how aggressive they choose to be for detecting disease in terms of human and economic cost-benefits) that suggests models of guessing (or chance).

There are other limits of the published literature that were reviewed. Many studies did not include qualitative criteria used by the readers to distinguish positive from negative F-18 FDG PET scans. When present, these criteria were included in the review. The majority of studies did not included information on how pathological diagnoses were made: how sampling was determined, who read the slides, how many readers per slide, were pathologists masked to imaging information, etc. Specimen sampling of mediastinal lymph nodes was described in detail by only one article, Vansteenkiste (1998). Lymphoma biopsy protocols were presented in detail by Carr (1998). Variations on how the pathological diagnosis was made may influence study results.

Also, many journals do not have space to devote to patient listings, although some articles did include detailed patient information ((Moog, 1998),(Friess, 1995),(Lowe, 1998)). Finally, the studies did not state a priori criteria for statistical parameters: type I error, type II error, and power. Were these limits encountered in a new drug application, a usual recourse would be to obtain clarification or more data from the sponsor. While many of the published studies may have, in fact, all the information, processes, and procedures cited here as absent, unfortunately this review has no means to assess that.

Most patients were selected after having been diagnosed with an abnormal test leading up to biopsy or were already diagnosed with cancer and having follow-up for recurrence. These populations are appropriate in testing the performance of F-18 FDG PET's diagnostic capacity. The studies reviewed show F-18 FDG PET has effectiveness in detecting malignancy in these populations. No prospective studies about efficacy of F-18 FDG PET for population screening were found or reviewed. Therefore, use of F-18 FDG PET in population screening for malignancy has not been determined to be safe or effective by this review.

Some studies, Delbeke (1998), Lowe (1994), Valk (1995), used CT for localization of the lesions to identify regions of interest for SUV analysis. This may have biased the readings of the F-18 FDG PET images. However, F-18 FDG PET may be used as a follow up test to CT scans when results are indeterminant. In that case, the use of CT scans with F-18 FDG PET may be acceptable in the study design. This review also included studies that performed SUV region of interest identification without CT on PET images or with CT but as a separate procedure from qualitative visual interpretation (Avril (1996), Moog (1998), Schiepers (1995), Bury (1997) Lowe (1998), Vansteenkiste (1998), Gupta (1996), Sazon (1996)).

Interpretations of CT scans and other tests, such as bone scans, may not have been under the control of the study authors. Because some studies did not explicitly publish how non-PET image interpretations were obtained, there may be variations on how these tests were read: some studies may have used interpretations from outside referring practices and other studies may have re-read these images as part of the study. For example, Valk (1995) and Sazon (1996), did reinterpret these other imaging scans as part of their study protocol. Despite the possibility of variation of how interpretations were obtained, the results appear to still be consistent in supporting the performance of PET imaging.

One study did not indicate whether CT was used or not with PET interpretation (Friess (1995)). The studies which used CT scans in conjunction with F-18 FDG PET image assessment or compared performance of F-18 FDG PET and CT did not always mention if the CT scans were performed with oral or intravenous contrast or both. Although the assumption may be that intravenous contrast is often used in oncology imaging, this absence of stated information about the CT scans makes limits comparison of CT results across the studies.

Verification of distant metastases is inherently a problem in diagnostic test evaluations. It is hard to obtain pathology on all "test positive" lesions found by conventional imaging and F-18 FDG PET. In addition, follow up of all negative test results to ensure true negativity is also hard because the duration of follow-up may need to be years. All reviewed studies did biopsy patients based on their conventional imaging abnormality. This would be appropriate as conventional imaging is the standard of practice. One study did biopsy F-18 FDG PET positive cases in which conventional imaging was negative (Holder, 1998) but this process is biased in favor of the new technology because its leads to either improvement or unchanged sensitivity. There is no potential to decrease the sensitivity of the new technology using this form of discrepancy resolution. However, this review does include studies with follow up of from 7 to 25 months to ensure negative results were true (Schiepers (1995) and Friess (1995)).

Timing of when F-18 FDG PET was performed relative to when definitive histology was obtained was acceptable in the reviewed studies that stated the time frame. The time frame was short to prevent affects of time on clinical presentation. Because F-18 FDG PET was performed prior to biopsy in all studies except the lymphoma bone marrow and breast cancer axillary node studies, those studies that did not state a time frame most likely had biopsies performed in a relatively short time frame to meet clinical practice standards of diagnosing malignancy.

Two studies used intravenous furosemide, Lowe (1994) and Friess (1995), and one study, Holder (1998), used intravenous diazepam. Furosemide is an inhibitor of sodium, potassium, and chloride symport in the thick ascending limb of the loop of Henle. It can also inhibit glycolysis and may cause hyperglycemia. Diazepam is a benzodiazepine intravenous anesthetic with no known affect on glucose

metabolism. More information, referred to in the studies as unpublished data, should be presented to ensure no adverse affect of furosemide on PET imaging.

The F-18 FDG PET imaging literature in oncology has been reviewed systematically by the Veterans Health Administration (VHA) in October 1996 and by the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) in March 1997. These reports' conclusions differ from this FDA medical review of the F-18 FDG PET imaging literature in oncology because the statutory requirement for substantial evidence of safety and effectiveness differs from the criteria used by these other organizations. The FD&C does not mandate drug approval based on criteria requiring incremental value of PET information on treatment planning, health outcomes, or clinical utility of PET in selected conditions relevant to the veteran population.

The TEC criteria stated in the report are: 1) the technology must have final approval from the appropriate governmental regulatory bodies (FDA), 2) the scientific evidence must permit conclusions regarding the effect of the technology on health outcomes, 3) the technology must improve the net health outcomes, 4) the technology must be as beneficial as any established alternatives, and 5) the improvement must be attainable outside the investigational setting. The report concluded that for five specific indications related to differential diagnosis of intracranial masses, differentiation of low-grade and high-grade brain tumors, for the guidance of stereotactic biopsy or biopsies of intracranial mass, differentiation of recurrent brain tumor from radionecrosis, or for monitoring response to treatment in patients with brain tumors, PET does not meet the TEC criteria. The TEC report implies that criteria 2-5 differ from criteria 1, FDA approval. In fact, criteria 2-5 are outside the statutory mandates for evaluation of effectiveness established by the FD&C.

The VHA review of the F-18 FDG PET literature in diagnosing cancer concluded that "the knowledge base supporting clinical diagnostic applications of PET has significant deficiencies" and that the "usefulness and contribution to improved outcomes" has not been adequately evaluated to support the VHA's establishment of additional PET centers. The review cited several problems with the PET literature of 1991-1995, the time period of the articles. These problems include retrospectively analyzed case series data, small patient numbers, uneven numbers of cases and controls, lack of control group, and lack of masking the image interpreters or lack of addressing interobserver variation. The VHA

review also discussed VHA specific issues relating to difficulties in supporting and maintaining the cost of this technology. This FDA medical review of safety and efficacy data focused on whether substantial evidence for effectiveness, as defined by the FD&C and its implementing regulations and legislative history, is present in the current literature. Many of the weakness of studies that the VHA identified have been addressed. Only articles that had a prospectively enrolled population, utilized pathology as a standard of truth, and, as a group, had numbers of cases or lesions that were useful in assessing test performance are included in this review. While the number of subjects varied in the studies, only studies having fifty or more patients were reviewed. Many of the studies had mechanisms to reduce bias, such as masking. This medical review contains only three of the 35 studies the VHA originally included in their oncology review in 1996. An updated VHA report is due in 1999.

This review finds that multiple, prospective clinical studies conducted by different investigators produced consistent results that support the clinical use of F-18 FDG PET to detect increases of glucose metabolism for the evaluation of malignancy in patients with abnormalities found by other imaging modalities and in patients with an existing diagnosis of cancer. The studies reviewed all compared F-18 FDG PET results to histologic standards of diagnosis. The findings from the cumulative F-18 FDG PET literature for the reviewed cancer types are robust and the functional aspect of the test is applicable to cancer in general. As such, this review supports the use of F-18 FDG PET to detect abnormal glucose metabolism to assist in the evaluation of malignancy in patients with abnormalities found by other imaging modalities, or patients with an existing diagnosis of cancer. The limitations of the studies should be reflected in the labeling of the product. The label should also state that F-18 FDG PET results are not diagnostic for a specific type of malignancy and there are limits to its sensitivity and specificity. F-18 FDG does not replace the need for histopathology for diagnosis.

III. Safety Evaluation

F-18 FDG PET radiopharmaceutical is radioactively labeled fluorine analog of glucose. It is administered intravenously for PET imaging. The overall distribution, metabolism, and excretion of F-18 FDG PET is well understood after roughly two decades of use. A dose of 185-370 MBq(5-10 mCi) of F-18 FDG was approved by FDA in 1994 for PET imaging to identify regions of abnormal glucose metabolism with foci

of epileptic seizures with this same dosimetry information. No adverse reactions have been reported from this use.

In the reviewed F-18 FDG PET studies, patients generally fasted for 4 or more hours before imaging in an effort to reduce serum insulin levels to near basal levels. This is important because insulin can direct F-18 FDG away from the blood and into muscle and fat. In addition, the fasting state minimizes competitive inhibition of F-18 FDG uptake. Following this, patients were injected with about 200 740 MBq of F-18 FDG intravenously and imaging usually began 30-101 minutes after injection. The effects of diabetes and serum hyperglycemia on the uptake of F-18 FDG have not been studied adequately. A few studies, Holder (1998), Dietlein (1997), Vansteenskiste (1998), excluded diabetic patients or they were restudied when fasting glucose was less than 100 mg/dl. In the approved labeling for F-18 FDG for epileptic foci diagnosis with PET, it states, "Diabetic patients may need stabilization of blood glucose on the day preceding and on the day of the F-18 FDG scan."

The physical half-life of F-18 FDG is 109.8 minutes. Once injected, it is rapidly distributed to all organs of the body. F-18 FDG is taken up by cells and phosphorylated to F-18 FDG-6-phosophate at a rate proportional to the rate of glucose utilization within a given tissue. F-18 FDG-6-phosophate presumably is metabolized to 2-deoxy-2-[F-18]fluoro-6-phospho-D-mannose and [F-18]FDM-6-phosphate. [F-18]FDG contains 2-deoxy-2-cholor-D-glucose (ClDG) as a known impurity. Distribution and metabolism of this is presumable similar to that of F-18 FDG. The phosphorylated deoxyglucose compounds are dephosphorylated, and the resulting compounds, including those related to ClDG, presumably leave cells by passive diffusion. F-18 FDG and related compounds are largely excreted unchanged in the urine within 3 to 24 hours (except from cardiac tissue, which may require more than 96 hours). Unlike glucose, F-18 FDG and related compounds are not reabsorbed in the renal tubules. Dosimetry data from the literature and from the previously approved new drug application for F-18 FDG has been evaluated by the biopharmacologist. For an average dose of 370 MBq (10 mCi) of F-18 FDG, the target organ (the bladder) absorbs 6.29 rads based on a fixed bladder content over a three hour period of time. Increasing the voiding frequency and bladder capacity (250cc) brings the exposure down to 3 rads in adults. Thus, for higher doses, the level and extent of radiation absorbed by the bladder walls can be manipulated with hydration and shorter voiding intervals to decrease radiation exposure.

The dosimetry data mentioned above are the same data that were acceptable for F-18 FDG's approval in 1994. Therefore, for a labeled dose based on the literature review the averaged dose from the studies of 370 MBq can be recommended.

For a dose of 370 MBq (10mCi), the typical quantity of F-18 FDG is <1.5 micrograms, sodium chloride is 198 mg, glucose ≤8 mg and 2-chloro-2-deoxy-D-glucose of less than 0.1 mg. For doses to 25 mCi, increasing these amounts by 1.5 fold is still acceptable for human use.

In the published literature concerning safety of PET drugs, in 1996, Edward Silberstein, Janet Ryan and the Pharmacopeia Committee of the Society of Nuclear Medicine published in the Journal of Nuclear Medicine in a five year prospective study of 18 collaborating institutions using a questionnaire which enumerated monthly the number of procedures used and the adverse reactions noted for radiopharmaceuticals and non-radioactive drugs used in nuclear medicine. The study utilized operational definitions for adverse reactions and significant adverse reactions and devised an algorithm to categorize probability of causation. The published study included a copy of the actual questionnaire, which required itemization of any and all radiopharmaceuticals administered, adverse reactions to radiopharmaceuticals, dose, route, reaction, etc., as well as total non-radiopharmaceuticals (such as adenosine or dipyridamole) administered and adverse reactions to these agents. NO reactions are reported for F-18 FDG PET. The study also performed a reference check of listed adverse reactions by references and no adverse reactions were listed by the U.S. Pharmacopeial Convention's Drug Information for the Health Care Professional, 1995. Dr. Silberstein and the Pharmacopeia Committee of the Society of Nuclear Medicine also conducted a retrospective and prospective study of the prevalence of adverse reactions to PET radiopharmaceuticals published in 1998 in the Journal of Nuclear Medicine. Dr. Silberstein reported 22 PET centers provided monthly adverse reaction data from 1994 to 1997 related to PET drug administration in 47,876 dosages. In addition, retrospective data was collected from the opening of these centers on 33,925 radiopharmaceutical dosages. In no case were there any adverse reactions.

The published clinical trials literature is not an appropriate data base to evaluate chemistry and manufacturing safety issues related to drug purity and identity. Different production pathways may lead to different concentrations of F-18 FDG and to different by-

products and impurities. These specific topics will be addressed by the FDA PET Chemistry and PET Good Manufacturing Practice working groups.

Because radiation is a known carcinogenic and mutagenic agent, standard radiation precautions for using F-18 FDG PET with respect to patients, pregnant women, and occupational exposure are needed.

IV. Conclusions

The well-controlled studies of Lowe (1998) and Carr (1998) permit estimates of sensitivity and specificity of F-18 FDG PET performance for assessing malignancy in patients with abnormalities found by another imaging modality and in patients with an existing diagnosis of malignancy. The supportive studies included in this review provide independent corroboration of the increased glucose metabolism in association with a variety of other malignancies. However, the test's sensitivity is restricted by biologic variability of cancer glucose utilization such that false negative examinations may occur. Furthermore, increased glucose utilization is not restricted to malignant cells. Therefore, F-18 FDG PET imaging does have limitations in specificity. In the reviewed studies, the sensitivity and specificity varied with the type of cancer, size of cancer, and other clinical parameters. The trial designs and hypotheses tested did not study how F-18 FDG might be used prospectively. However, given the long history of use of F-18 FDG PET and the numbers of studies showing consistent findings, these studies collectively demonstrate the clinical relevance of performing F-18 FDG studies in patients with suspicious abnormalities from other testing modalities or pre-existing diagnoses of cancer. However, more studies would be needed if labeling claims were to contain cancer-specific diagnostic or management claims.

All the studies reviewed were diagnostic studies, not population screening studies. The studies did have well-defined populations in which effectiveness was derived: patients with abnormalities on another imaging modalities, such as x-ray or CT scan, or patients with an existing diagnosis of cancer. These populations are sufficiently different from other types of populations to not permit generalization of results to other populations. As such, this review finds effectiveness for those specifically studied populations, namely, patients undergoing diagnostic evaluation for known abnormalities, not population

screening. Safety information reveals manageable radiation risk and unknown performance and risk to patients with diabetes. In summary, F-18 FDG PET may provide additional information based on glucose metabolism to assist physicians in the evaluation of malignancy in patients with abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer.

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References

Avril N, Dose J, Janicke F, Sense S, Ziegler S, Laubenbacher C, Romer W, Pache H, Herz M, Allgayer B, Nathrath W, Graeff H, Schwaiger M. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. J Clin Oncol 1996;14:1848-57.

Bury T, Dowlati A, Paulus P, Corhay JL, Hustinx R, Ghaye B, Radermecker M, Rigo R. Whole-body 18-FDG positron emission tomography staging of non-small cell lung cancer. Eur Respir J 1997;10:2529-2534.

Carr R, Barrington SF, Madan B, O'Doherty MJ, Saunders CAB, van der Walt J, Timothy AR. Detection of lymphoma in bone marrow by whole-body positron emission tomography. Blood 1998;91:3340-46.

Delbeke D, Martin WH, Sandler MP, Chapman W, Wright Jr K, Pinson W. Evaluation of benign vs malignant hepatic lesions with positron emission tomography. Arch Surg 1998;133:510-516.

Dietlein M, Scheidhauer K, Voth E, Theissen P, Schicha H. Fluorine-18 fluorodeoxyglucose positron emission tomography and iodine-131 whole-body scintigraphy in the follow-up of differentiated thyroid cancer. Eur J Nucl Med 1997;24:1342-48.

Friess H, Langhans J, Ebert M, Beger HG, Stollfuss J, Reske SN, Buchler MW. Diagnosis of pancreatic cancer by 2[18-F]-fluoro-2-deoxy-D-glucose positron emission tomography. Gut 1995;36:771-777.

Gupta NC, Maloof J, and Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. J Nucl Med 1996;37:943-948.

Holder Jr. W, White RL, Zuger JH, Easton Jr. EJ, Greene FL. Effectiveness of positron emission tomography for the detection of melanoma metastases. Annals of Surg 1998;227:764-771.

Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirchner P, Valk P, Karis J, Hubner K, Delbeke D, Heiberg EV, Patz EF, Coleman

RE. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol 1998;16:1075-1084.

Lowe VJ, Hoffman JM, DeLong DM, Patz Jr. EF, Coleman RE. Semiquantitative and visual analysis of FDG-PET images in pulmonary abnormalities. J Nucl Med 1994;35:1771-1776.

Meyer GJ, Waters SL, Coenen HH, Luxen A, Maziere B, Langstrome B. PET radiopharmaceuticals in Europe: current use and data relevant for the formation of summaries of product characterizatics (SpCs). Eur J Nucl Med 1995;22:1420-32.

Moog F, Bangerter M, Kotzerke J, Guhlmann A, Frickhofen N, Reske SN. 18-F-fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. J Clin Oncol 1998;16:603-9.

Sazon DA, Santiago SM, Soo Hoo GW, Khonsary A, Brown C, Mandelkern M, Blahd W, and Williams AJ. Fluorodeoxyglucose-positron emission tomography in the detection and staging of lung cancer. Am J Respir Crit Care Med. 1996;153:417-21.

Schiepers C, Penninckx R, De Vadder N, Merckx E, Mortelmans L, Bormans G, Marchal C, Filez L, Aerts R. Contribution of PET in the diagnosis of recurrent colorectal cancer: comparison with conventional imaging. Euro J of Surgical Oncology 1995;21:517-522.

Silberstein EB, Ryan J, and the Pharmacopeia Committee of the Society of Nuclear Medicine. Prevalence of adverse reactions in nuclear medicine. J Nucl Med 1996;37:185-92.

Silberstein EB and the Pharmacopeia Committee of the Society of Nuclear Medicine. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. J Nucl Med 1998;39:2190-2.

Utech C, Young CS, Winter PF. Prospective evaluation of fluorine-18 fluorodeoxyglucose positron emission tomography in breast cancer for staging of the axilla related to surgery and immunocytochemistry. Eur J Nucl Med 1996;23:1588-93.

Valk PE, Pounds TR, Hopkins DM, Haseman MK, Hofer GA, Greiss HB, Myers RW, Lutrin CL. Staging Non-small cell lung cancer by whole-body positron emission tomographic imaging. Ann Thorac Surg 1995;60:1573-82.

Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Bogaert J,, Maes A, Deneffe GJ, Nackaerts KL, Verschakelen JA, Lerut TE, Mortelmans LA, Demedts MG. Lymph node staging in non small cell lung cancer with FDG-PET scan: a prospective study of 690 lymph node stations from 68 patients. J Clin Oncol 1998;16:2142-2149.