Semiquantitative and Visual Analysis of FDG-PET Images in Pulmonary Abnormalities

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FDG PET images of the thorax can be analyzed semiquantitatively using standardized uptake ratios (SUR) or activity ratios between abnormal and normal tissue, or qualitatively by visual comparison of the abnormality to normal structures. Standardized uptake ratio evaluation of FDG PET images has been shown to accurately differentiate benign from malignant focal pulmonary abnormalities. The accuracy of activity ratios and visual analysis have not been evaluated. We therefore prospectively analyzed FDG PET images in patients with pulmonary abnormalities to evaluate differences in analytic schemes. **Methods:** We evaluated 107 patients with an indeterminate focal abnormality on chest radiograph or CT with FDG PET between November 1991 and March 1993. The PET studies were evaluated using SUR, activity ratios and visual analysis. Activity ratios of maximum activity/cc and average activity/cc between regions of interest (ROIs) in abnormalities and normal lung on the contralateral side were calculated. Visual interpretations were graded on a five-point scale of two observers' confidence of malignancy. FDG uptake in the abnormality was also visually graded in comparison to mediastinal activity. Receiver-operating characteristic (ROC) curve areas were generated for the SUR data, activity ratios and visual analysis. **Results:** Of 88 patients in which a conclusive diagnosis was made, 61 (69%) patients had malignancy and 27 (31%) patients had a benign process. SUR, maximum activity ratio, average activity ratio and visual interpretation ROC curve areas were 0.96, 0.95, 0.92 and 0.96, respectively. **Conclusions:** SUR, activity ratios and visual evaluation are each equally accurate methods of FDG PET data analysis in differentiating malignant from benign focal pulmonary abnormalities.

Key Words: PET; fluorine-18-FDG; lung neoplasms

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Metabolic differences between benign and malignant tissue can be utilized to develop imaging techniques to detect malignancy using PET (*1–3*). Cancer cells have increased glucose metabolism related to their rapid cell proliferation. The uptake of ^{18}F-fluorodeoxyglucose (FDG) as a glucose analog and its subsequent phosphorylation and trapping within cells provides a method for evaluating glucose metabolism of tumor cells (*4*).

Focal pulmonary abnormalities such as solitary pulmonary nodules (≤4 cm), pulmonary masses (>4 cm) and poorly marginated opacities may suggest the presence of malignancy. CT and MRI provide anatomic and morphologic information, but cannot reliably distinguish malignant from benign lesions and many lesions remain indeterminate following conventional evaluation (*5,6*). Definite diagnoses are often established with bronchoscopic or percutaneous biopsy. The sensitivities and specificities of these tests vary from 71% to 93% and 91% to 96%, respectively (*7–11*). Inherent in invasive procedures are patient morbidity and high cost. Pneumothorax is reported to occur in 20% of percutaneous biopsy cases. Although pneumothorax resolution is generally spontaneous, a few cases require hospitalization or chest tube placement (*7,12*). In cases that are nondiagnostic (40% in some series) (*11*), patients must proceed to thoracotomy for diagnosis by open biopsy.

Preliminary studies have demonstrated the utility of PET in oncologic imaging (*13*). Statistically significant increased FDG uptake in lung cancer has been demonstrated (*14–16*). Quantitative studies have documented a sixfold greater metabolic rate in bronchogenic carcinoma than in normal lung (*13*). Recent studies evaluating the utility of FDG PET imaging in patients with solitary pulmonary nodules have demonstrated accurate differentiation between benign and malignant abnormalities (*17,18*). Preliminary data on the ability of FDG PET to accurately stage bronchogenic carcinoma has been reported (*15*). Other positron-emitting agents such as ^{11}C-labeled methionine have been used successfully in evaluating lung cancer (*19–21*).

Data obtained from PET studies can be evaluated in several different ways, although to date there is no uniform method for analyzing this information. In this study we compare different methods of FDG PET data analysis to determine the accuracy of each technique in distinguishing benign from malignant pulmonary abnormalities.

METHODS

Patients

Between November 1991 and March 1993, 107 patients found to have radiographically indeterminate focal pulmonary abnormalities were referred for FDG PET imaging. All patients fasted at

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least 4 hr prior to the PET study. PET imaging of these patients was approved by the Institutional Review Board of our hospital. Informed consent was obtained from all patients who participated in the study.

PET Imaging

FDG PET imaging was performed on a GE 4096 Plus (GE Medical Systems, Milwaukee, WI) which produces 6.5-mm thick image planes (8 direct planes and 7 cross planes). Full width at half maximum (FWHM) is 5 mm. The axial field of view is 10.3 cm.

The ^{18}F-fluoride is produced by a CS-30 cyclotron (CTI, Berkeley, CA) facility. The ^{18}F-fluoride ions are transferred to either a CTI-Berkeley or General Electric automated system for synthesis of ^{18}F-FDG. FDG was tested for sterility, pyrogenicity, and radiochemical purity on each production run.

Transmission scans using a rotating ^{68}Ge pin source were performed on all patients either prior to injection of FDG or prior to emission image acquisition. Emission images of the region of radiographic abnormality were obtained 30 min after intravenous injection of 10.0 mCi of FDG and were acquired for 20 min to obtain approximately 1 million counts per plane.

Transmission images were reconstructed using filtered backprojection smoothed with a Hann window of 7.0 mm width. Emission images were reconstructed using filtered backprojection with a Hann window 5.0 mm wide. Emission data were corrected for scatter, random events and deadtime. Image pixel size was 3.0 mm in a 128 × 128 array.

Data Analysis

A nuclear medicine physician (VJL) and chest radiologist (EP) used CT and chest radiographs to locate abnormalities on FDG-PET images. Regions of interest were placed over the most intense area of FDG accumulation (2.7 ± 1.4 cm^2). After correction for radioactive decay, the ROIs were analyzed by computing standardized uptake ratios (SUR) according to the following formula:

$$\text{SUR} = \frac{\text{mean ROI activity (mCi/ml)}}{\text{injected dose (mCi)/body wt (g)}}.$$

Activity ratios were calculated between lesions and homologous contralateral normal lung for average, as well as maximum activity/cc values. ROIs were determined without knowledge of biopsy results. No partial volume correction was applied.

Two nuclear medicine physicians (JH, EC) blinded to biopsy results and anatomical data were shown transmission and emission images. 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 FDG uptake 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) and graded lesion FDG uptake compared to mediastinal uptake (on a five-point scale with 5 >> mediastinum, 4 > mediastinum, 3 = mediastinum, 2 < mediastinum, 1 << mediastinum). Anatomical information (chest radiograph and CT scan) was then given to the nuclear medicine physicians who then individually regraded the PET study. 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-operator characteristic curves were then generated for the different techniques of evaluation using a nonparametric approach (*22*).

RESULTS

Of the 107 patients imaged, a definitive diagnosis had been made in 93 patients at the time of this study. Three of these patients had unretrievable data on the PET data storage discs and two patients had technical problems related to patient positioning for the PET scan. The PET studies from the remaining 88 patients were evaluated. Ten patients had poorly marginated opacities and in the remaining 78 patients, the mean abnormality size was 2.5 ± 1.1 cm. Six of the 78 patients had pulmonary masses (>4 cm) and the remaining 72 had pulmonary nodules (≤4 cm), of which 9 were ≤1.2 cm. In the 88 patients, a diagnosis was made by either bronchoscopy, transthoracic thin-needle aspiration (TTNA), thoracotomy or radiographic stability for more than 8 yr (1 patient). Sixty-one patients had malignancies and 27 patients had benign processes.

In the patients who had no definite clinical diagnosis, six were being followed by chest radiograph, two developed contraindications to biopsy, two had biopsies performed after they left our institution and the results could not be obtained, one was lost to follow-up, two had no evidence of cancer and no other definitive diagnosis on bronchoscopy and one had TTNA without an adequate sample.

Of the 88 patients evaluated, four were known to have type II diabetes mellitus and none of the other patients had a history of diabetes mellitus. Blood glucose values at the time of the PET study were obtained on the last 22 patients.

Examples of malignant and benign lesions are seen in Figures 1 and 2. Areas under ROC curves, their standard deviations and 95% confidence intervals are shown in Table 1. The area under the ROC curve for SUR (0.96) and consensus confidence of malignancy using visual analysis and anatomical studies (0.96) were not statistically different ($p = 0.35$). Areas for the maximum activity ratio and the average activity ratio were 0.95 and 0.92, respectively ($p = 0.1$).

The area under the ROC curve for visual grading of FDG uptake relative to mediastinal uptake was 0.92 for Reader 1, 0.94 for Reader 2 and 0.95 for the consensus. The evaluation of the PET images by confidence of malignancy using visual analysis without anatomical studies had areas for both readers of 0.93 that improved minimally to 0.94 with anatomical information ($p = 0.11$ for Reader 1 and $p = 0.14$ for Reader 2).

When FDG uptake greater than that of mediastinum by visual analysis was considered to be positive for malignancy, the sensitivity and specificity of the test was 97% and 89%, respectively.

DISCUSSION

FDG PET evaluation of focal pulmonary abnormalities differentiates benign from malignant disease (*17,18,23*). CT and MRI provide anatomic and morphologic information, but cannot reliably distinguish malignant from benign lesions (*6,24,25*). CT and MRI staging of bronchogenic car-

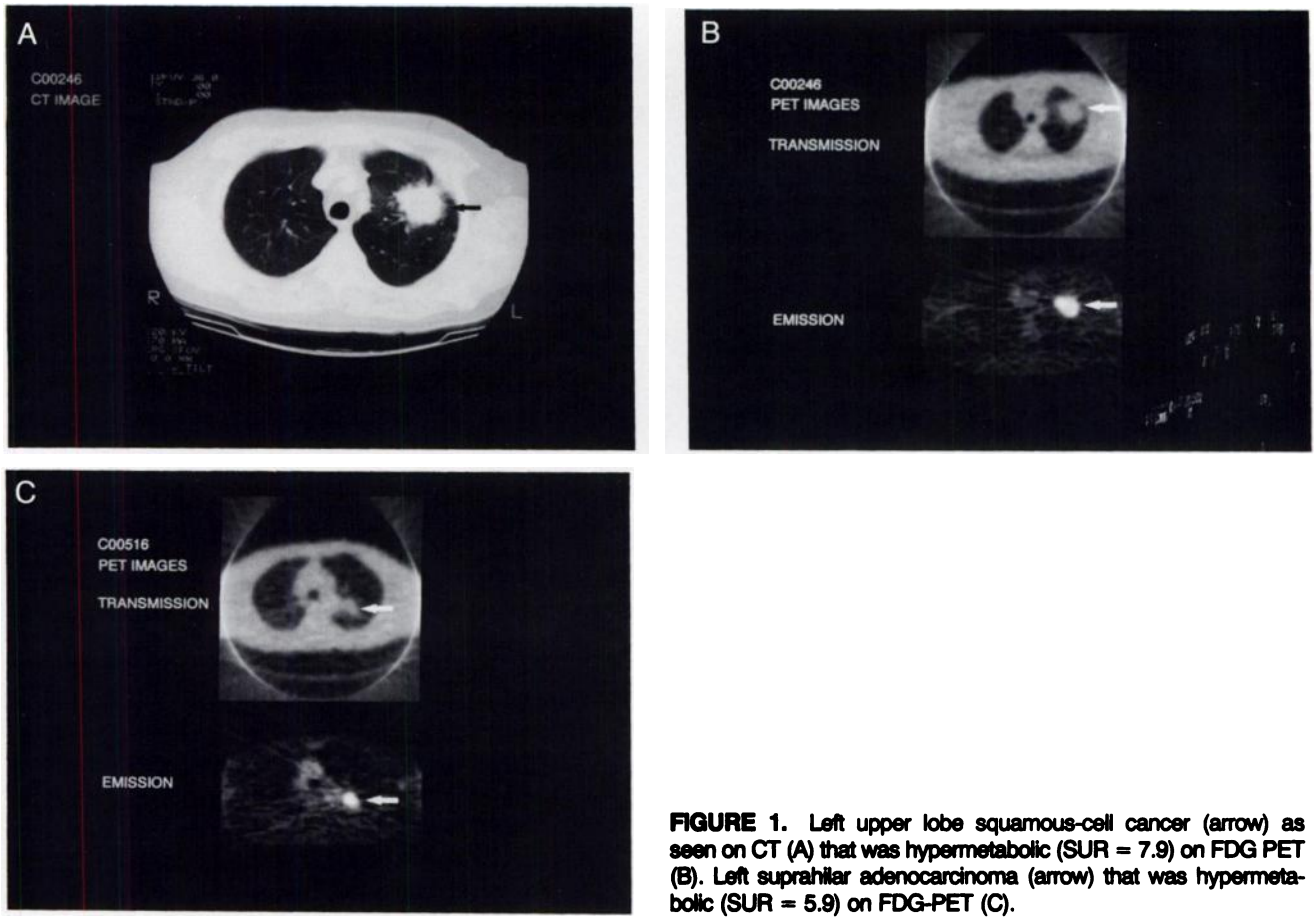

FIGURE 1. Left upper lobe squamous-cell cancer (arrow) as seen on CT (A) that was hypermetabolic (SUR = 7.9) on FDG PET (B). Left suprahilar adenocarcinoma (arrow) that was hypermetabolic (SUR = 5.9) on FDG-PET (C).

cinoma have been reported to have a sensitivity of 25%–71% (*26–36*). Presently, clinicians rely on invasive diagnostic and staging methods (*37–40*). The potential of obtaining this information noninvasively has provided the impetus to explore techniques that can reduce the morbidity and the cost of invasive procedures.

It is unclear if SUR values provide the most accurate method of evaluating FDG PET data. Recent reports have described methods of calculating SUR values based on body surface area or lean body mass rather than weight (*41,42*). We evaluated several additional methods. We evaluated maximum and average activity/cc ratios between a focal pulmonary abnormality and an identical region in the contralateral lung. We also evaluated visual analysis of PET images. We instructed physicians to grade their confidence of malignancy in a study based on visual analysis and their knowledge of normal FDG uptake within the thorax. To specifically identify a reference structure by which physicians can guide visual interpretation, we had the readers grade lesion uptake as it compared to mediastinal uptake.

Standardized uptake ratio evaluation and visual analysis using anatomical information were shown to produce nearly identical areas on ROC curve analysis and had the largest ROC curve areas of the PET data analysis methods evaluated. Ratios of maximum activity (0.95) had slightly larger areas than ratios of average activity (0.92) ($p = 0.1$). Visual evaluation of PET data without the use of any anatomical data also demonstrated good accuracy in differentiating malignant and benign disease. Each reader's ROC curve area changed insignificantly when anatomic information by chest radiographs or CT was provided ($p = 0.11$ for Reader 1 and $p = 0.14$ for Reader 2).

We did not apply partial volume correction in the data analysis. Nine nodules were ≤1.2 cm in our patient group. Ongoing phantom work at our institution has shown that 1.2 cm lesions have approximately a 20% activity measurement loss because of partial volume effects. All nine of these lesions (four malignant and five benign lesions) were correctly identified by SUR without the use of partial volume effect correction.

The transmission scans seen in the cases in Figures 1 and 2 demonstrate pulmonary masses. Focal abnormalities can be visualized on the majority of transmission scans. When the abnormalities were difficult to identify on the transmission scan, and were not clearly identifiable on the emission scan, visual interpretation without the aid of other anatomical data was difficult. This only occurred rarely as can be seen by the minimal gain in ROC curve areas when anatomical information was provided. Therefore, PET data alone provided adequate information in all but a few cases. Lesions in the mediastinum or abnormalities adjacent to

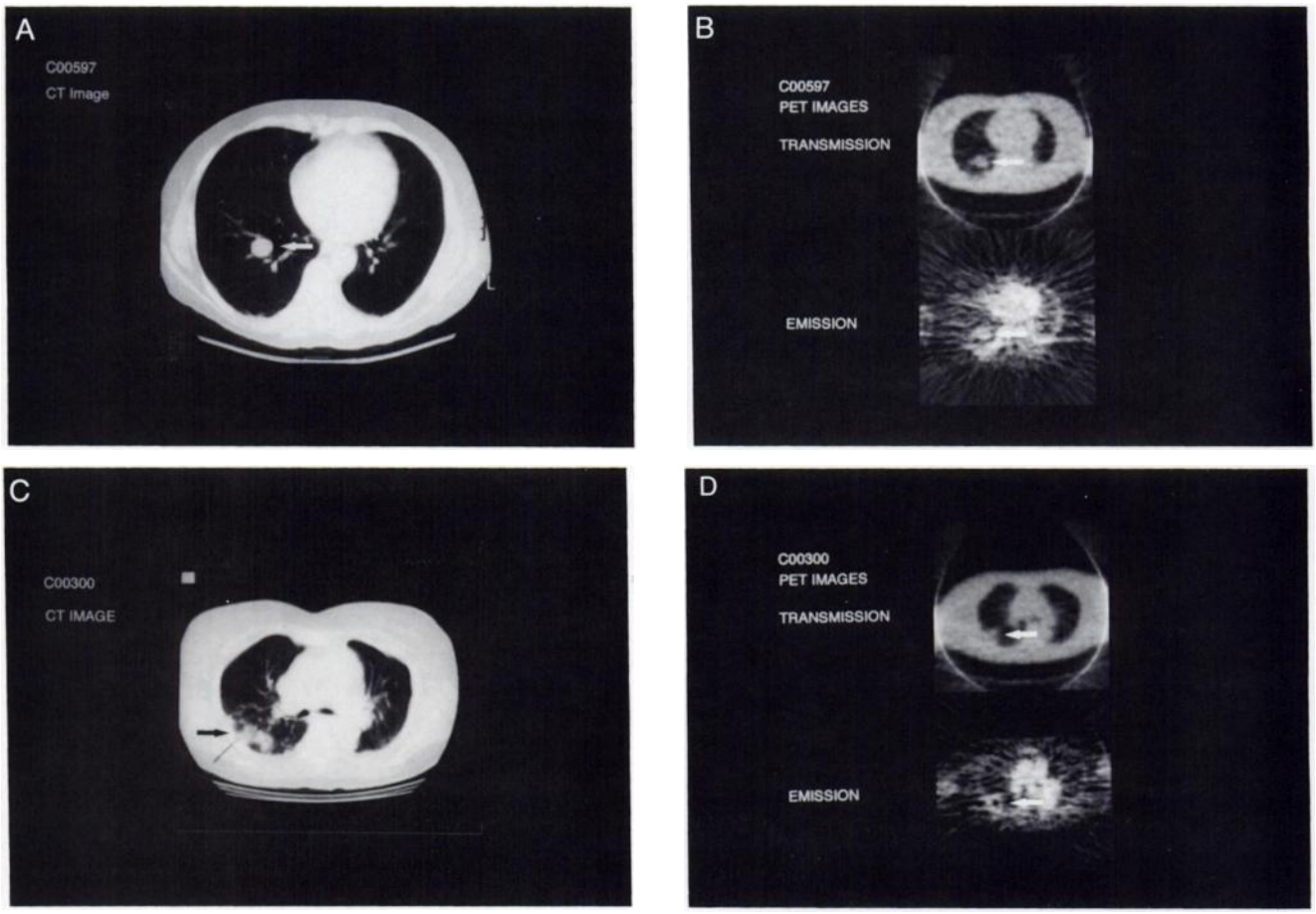

FIGURE 2. Right mid lung hamartoma (arrow) as seen on CT (A) that was hypometabolic (SUR = 2.1) on FDG-PET (B). Right lung posterior lateral resolving pneumonia (arrow) on CT (C) that was hypometabolic (SUR = 1.3) on FDG-PET (D).

soft-tissue structures would fall into this category, although we did not image mediastinal masses in this protocol.

This study shows that FDG uptake in the mediastinum can be used as an accurate reference for visual interpretation. The assessment of probably or definitely tumor as used in the five-point scale involves a multifactorial decision process related to prior experience, knowledge of normal uptake distributions, morphology, etc. and is somewhat subjective although useful in ROC curve analysis. We have found that mediastinal blood pool regions generally have an SUR of about 2.0–2.5 but can vary depending on ROI placement. We evaluated the lesion uptake relative to the mediastinum to provide a distinct reference for assessment. Lesion FDG uptake greater than that of the mediastinum most likely represents a malignant process. When uptake greater than that of the mediastinum was considered to be positive for malignancy, the sensitivity and specificity of the test was 97% and 89%, respectively.

Eight cases were read as equivocal by the individual readers. In these cases only one was read as equivocal by both readers. The consensus remained equivocal in five of the eight cases. Two of the eight cases were malignant. One of these had an SUR of 3.1 and the other had an SUR of 2.0. It is therefore not clear that SUR data would have been more accurate in these malignant cases. The SUR may have added additional information in the negative cases as they all had SUR values that were less than 2.5.

Reports of variable or decreased FDG glucose uptake in patients who have elevated serum glucose levels prompted us to obtain glucose samples on patients prior to FDG injection (*43*). We started obtaining the samples during the last part of the study; thus, only 22 patients have correlative glucose values and therefore no analysis of this data was performed. Of the four patients who had diabetes (all had type II) in our study, all were correctly identified by SUR (positive if >2.5) and visual interpretation (positive if 4 or 5).

CONCLUSION

FDG PET is highly accurate in differentiating benign and malignant focal pulmonary abnormalities. Visual interpretation of PET data when guided by anatomical imaging or semiquantitative analysis of PET data by either SUR analysis or ratios of uptake in abnormalities-to-normal tissue provide equivalent accuracy in evaluating focal pulmonary abnormalities. Visual interpretation of PET data without the use of anatomical information provides accurate iden-

TABLE 1
ROC Curve Areas

	ROC Variable	Area	Standard deviation	95% Confidence interval
Reader 1	Probability of tumor (no anatomical info)	0.93	0.03	0.86–1.00
	Probability of tumor (anatomical info)	0.94	0.03	0.88–1.00
	FDG relative to mediastinum (no anatomical info)	0.93	0.03	0.86–0.99
	FDG relative to mediastinum (anatomical info)	0.92	0.03	0.85–0.98
Reader 2	Probability of tumor (no anatomical info)	0.93	0.03	0.87–0.99
	Probability of tumor (anatomical info)	0.94	0.03	0.88–1.00
	FDG relative to mediastinum (no anatomical info)	0.93	0.03	0.87–0.99
	FDG relative to mediastinum (anatomical info)	0.94	0.03	0.88–1.00
Consensus	Probability of tumor (anatomical info)	0.96	0.03	0.90–1.00
	FDG relative to mediastinum (anatomical info)	0.95	0.03	0.90–1.00
Semiquantitative	Average activity ratio	0.92	0.03	0.85–0.98
	Maximum activity ratio	0.95	0.03	0.90–1.00
	SUR	0.96	0.02	0.91–1.00

tification of malignancy in focal pulmonary abnormalities although this may be improved slightly with the use of anatomical information.

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