PET in Lung Cancer*

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An estimated 180,000 new cases of lung cancer will be diagnosed in the U.S. this year, and lung cancer accounts for approximately 25% of all cancer deaths. Most lung cancers are initially detected on chest radiographs, but many benign lesions have radiologic characteristics similar to malignant lesions. Thus, additional studies are required for further evaluation. CT is most frequently used to provide additional anatomic and morphologic information about lesions, but it is limited in distinguishing between benign and malignant abnormalities. Because of the indeterminate results obtained from anatomic images, biopsy procedures, including thoracoscopy and thoracotomy, may be used even though one half of the lesions removed are benign and do not need to be removed. Fluorodeoxyglucose (FDG) PET imaging provides physiologic and metabolic information that characterizes lesions that are indeterminate by CT, accurately stages the distribution of lung cancer and provides prognostic information. FDG PET imaging takes advantage of the increased accumulation of FDG in transformed cells and is sensitive (~95%) to the detection of cancer in patients who have indeterminate lesions on CT. The specificity (~85%) of PET imaging is slightly less than its sensitivity because some inflammatory processes, such as active granulomatous infections, avidly accumulate FDG. The high negative predictive value of PET suggests that lesions considered negative on the study are benign, biopsy is not needed and radiographic follow-up is recommended. Several studies have documented the increased accuracy of PET compared with CT in the evaluation of the hilar and mediastinal lymph-node status in patients with lung cancer. Whole-body PET studies detect metastatic disease that is unsuspected by conventional imaging and demonstrate some of the anatomic abnormalities detected by CT to be benign lesions. Management changes have been reported in up to 41% of patients on the basis of the results of whole-body studies.

Key Words: cancer; fluorodeoxyglucose; PET; diagnosis; staging

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The incidence of lung cancer is increasing globally (*1–3*). Death from lung cancer occurs at a higher frequency in men than in women. Lung cancer now claims approximately 150,000 lives each year in the U.S., and it claims more lives of women than does breast cancer. Several important determinants of variations in the incidence of lung cancer have been attributed to the prevalence of smoking in men and women, the type and amount of cigarettes smoked, age at initiation, the duration of smoking exposure and air pollution. Genetic predisposition and previous neoplastic lung disease are also among the risk factors for lung cancer.

New diagnostic and treatment strategies are needed if an impact is to be made on the survival rate of patients with lung cancer. The 5-y survival rate of patients with lung cancer is approximately 14% and has not changed over the past several decades despite aggressive treatment protocols (*4*). Patients who have lung cancer often present with solitary pulmonary nodules on chest radiographs obtained as preoperative evaluations or as part of routine physical examinations. Approximately one third of these solitary pulmonary nodules in persons 35 y or older are malignant. Solitary lesions in people younger than 35 y are much less likely to be malignant.

Chest radiography and CT are frequently performed on patients with suspected lung cancer. These modalities provide anatomic and morphologic information, but they do not accurately characterize abnormalities as benign or malignant. The diagnosis has required tissue obtained by sputum cytology or biopsy. More than 50% of radiographically indeterminate lesions resected at thoracoscopy are benign (*5*). Thus, an accurate method for noninvasively characterizing these lesions could result in the avoidance of unnecessary and expensive procedures that are not always diagnostic.

The ability of PET imaging using ^{18}F-2-fluoro-2-deoxyglucose (FDG) to exploit the biochemical differences between normal and neoplastic tissue has resulted in its routine use for characterizing lesions that are indeterminate by conventional imaging modalities and for staging the distribution of disease. The increased glucose metabolism of transformed cells results from several factors: increased expression of glucose transporter messenger ribonucleic acid, enhanced levels of glucose transporter proteins Glut1 and Glut3, high levels of hexokinase and downregulation of glucose-6-phosphatase enzymes (*6*). These processes result in the FDG-6-phosphate being trapped within the tumor cell and provide the basis for FDG PET tumor imaging.

LUNG CANCER CLASSIFICATION AND STAGING

The classification of lung cancer by the World Health Organization is widely accepted (*7*). Small cell lung cancer

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and non-small cell lung cancer (NSCLC) differ greatly, and the two groups of lung cancer are approached as malignancies distinct from each other (*7*). Small cell lung cancer has almost always spread systemically by the time of diagnosis. Surgery rarely results in cure, and chemotherapy is almost always used. Small cell lung cancer accounts for 17%–29% of all lung cancers.

Squamous cell carcinoma was once the most prevalent type of lung cancer in North America, and it now accounts for 30% of all lung cancers. It tends to be slow growing and requires 3–4 y before a tumor can be clinically detected from its beginning as an in situ carcinoma (*7*). Adenocarcinoma is now the most prevalent type of lung cancer in North America and accounts for 40% of all cases of lung cancer. Most adenocarcinomas are peripheral in origin. They can arise as peripheral scar tumors. Bronchoalveolar carcinoma differs from the other subtypes of adenocarcinoma because it presents in three different fashions: (a) a solitary peripheral nodule; (b) a multifocal disease; and (c) a rapidly progressive pneumonic form, which appears to spread from lobe to lobe, affecting both lung fields (*7*). Large cell carcinoma is the least common type of NSCLC and accounts for 15% of all lung cancers. The prognosis of patients with large cell undifferentiated carcinomas is similar to that of patients with adenocarcinomas (*7*).

Staging of lung cancer by the anatomic extent of the primary lung tumor (T), regional lymph nodes (N) and metastases (M) has been accepted and used worldwide in the management of lung cancer. TNM staging includes clinical, surgical and pathologic assessment. Clinical staging typically understages disease, compared with the final staging obtained at surgery and pathology. The 2-y survival rate is highly correlated with the stage of disease. For example, the 5-y survival rate in patients with stage I disease is 60%–80%, stage II disease is 25%–50%, stage IIIa disease is 10%–40%, stage IIIb disease is <5% and stage IV disease is <5%. Autopsy studies have found lung cancer metastases to be present in every organ system. The most frequent sites of metastatic disease from NSCLC are bone, the liver, adrenal glands and the brain (*7*).

Imaging studies have a primary role in the evaluation of patients with suspected lung cancer. A normal chest radiograph would indicate that lung cancer is unlikely. The presence of nodules and mediastinal and hilar changes suggestive of lymphadenopathy can be quite suggestive of malignancy. CT can detect smaller lesions than those detected by chest radiography, and CT can characterize some lesions as benign or malignant. The invasiveness of the tumor into the chest wall, vertebrae or mediastinum can be determined by CT, which can also be used to stage the extent of disease. Any lymph node >1 cm in diameter is considered abnormal and requires further investigation. CT can detect metastases to the liver and adrenal glands. The abnormalities detected by CT are generally nonspecific and require confirmation before being used in clinical management.

Percutaneous fine-needle aspiration biopsy of pulmonary nodules is used to obtain tissue for identification of malignancy in pulmonary nodules and other abnormalities detected by CT. The procedure is usually performed using CT guidance, and the positive yield has been reported to be as high as 95%. An indeterminate biopsy result must be further evaluated. A definite benign diagnosis is rarely made by this technique.

Bronchoscopy provides >90% diagnostic yield when a lesion is identified during this procedure. Peripheral lesions >2 cm in diameter can be reached by brushes, needles or biopsy forceps, and tissue is obtained. Bronchoscopy is also useful in staging cancer because of the location of the cancer in the major airway as well as the ability to perform a biopsy on enlarged mediastinal lymph nodes.

The most accurate method for staging the superior mediastinal lymph nodes is mediastinoscopy. Anterior mediastinal lymph nodes are evaluated by the extended mediastinoscopic technique, by an anterior mediastinotomy or by video-assisted thoracoscopy. Video-assisted thoracoscopy has also been used to excise peripheral nodules and to evaluate pleural disease. Thoracotomy is used for diagnosis and staging in <5% of patients being evaluated for lung cancer because the less invasive procedures can provide the information necessary for patient management. On thoracotomy, unsuspected involvement of structures is frequently found and changes the stage of disease.

The role of radionuclide bone scanning in asymptomatic patients with early stage disease is controversial. Bone scanning has been advocated in clinical stage III disease before considering curative therapy (*7*).

FDG PET scanning is now being used in the evaluation of patients with focal pulmonary opacities on chest radiographs and in the staging of patients with lung cancer. PET scanning is now replacing some of the invasive procedures previously used in the evaluation of patients with lung cancer.

FLUORODEOXYGLUCOSE IMAGING

FDG imaging is performed while patients are in a fasting state to minimize competitive inhibition of FDG uptake by serum glucose (*8*). A 4-h fast is recommended. A 12-h fast may decrease accumulation by the myocardium and improve detection of mediastinal metastases. A serum glucose level is not obtained routinely before FDG administration at our institution. If there is a question concerning the duration of fasting or if there is the possibility of an elevated serum glucose level because of a history of glucose intolerance, a serum glucose level is obtained before FDG administration. In our facility, if the serum glucose level is <200 mg/dL, then FDG is administered. If the serum glucose level is >200 mg/dL, the study is delayed until the serum glucose level is <200 mg/dL. Administering insulin at the same time as FDG should be avoided because it leads to increased accumulation in skeletal muscle, and thus FDG is less available for accumulation in tumors. In patients with

diabetes who require an FDG scan, their blood sugar should be well controlled by either oral hypoglycemic agents or insulin, which should not be administered near the time of FDG administration. The administered FDG dose is 5.4 MBq/kg (145 μCi/kg), to a maximum of 740 MBq (20 mCi) for patients having studies on our dedicated PET scanner. Smaller doses are required for camera-based PET studies.

Lung cancer staging studies use whole-body imaging (*9*). Ideally, attenuation-corrected whole-body images should be obtained to provide more accurate detection of small lesions and lesions deep within the body. For a PET scanner with a 15-cm axial field of view, 10 bed positions are needed for a whole-body scan of an average adult. If 8- and 10-min transmission scans are obtained at 10 bed positions, a 3-h imaging study would be required. Segmentation of transmission scans is becoming available and allows transmission scans to be obtained in 1–2 min per bed position. Thus, attenuation-corrected whole-body scans can be obtained in approximately 100 min with these new techniques.

In a patient with lung cancer, our technique for a whole-body study using the General Electric Advance scanner (General Electric Medical Systems, Milwaukee, WI) begins 30 min after FDG injection with a 4-min brain scan using the three-dimensional acquisition mode (*10*). The three-dimensional mode is performed with the septa removed and provides an approximately fourfold increase in sensitivity for detection of annihilation radiation. There is an increase in scatter radiation in the three-dimensional mode compared with the two-dimensional mode, but the improved sensitivity provides better image quality. The scatter radiation in the body is greater than that in the head, and three-dimensional acquisition is not used for body imaging at this time. The system is switched to the two-dimensional acquisition mode after the brain scan is obtained, and nonattenuation-corrected scans are obtained for 4 min per bed position from the level of the base of the brain through the middle of the thighs. If a lesion is suspected or known to exist in the lower extremities, the acquisition will extend to the toes. This whole-body study at 8–12 bed positions requires 32–48 min of acquisition time. An attenuation-corrected regional chest scan at 2 bed positions is then obtained using 8 min for the emission scan and 10 min for the transmission scan at each bed position.

The FDG PET scans are interpreted qualitatively like other imaging studies, and an area of abnormality is detected by comparison with background activity. In the evaluation of a lung nodule, on attenuation-corrected images, the intensity of the accumulation in the nodule is compared with normal mediastinal and cardiac blood-pool intensity. If the accumulation in the nodule is greater than that in the blood pool, this finding indicates a malignant lesion. If the accumulation in the nodule is less than or equal to the mediastinal blood-pool activity, this finding suggests a benign lesion.

With attenuation-corrected FDG imaging, a semiquantitative parameter may be useful in characterizing lesions as benign or malignant. This semiquantitative parameter is an index of glucose metabolism called the standardized uptake ratio (SUR), which is also referred to as the standardized uptake value (*11,12*). The SUR normalizes the amount of FDG accumulation in a region of interest (ROI) to the total injected dose and the patient's body weight. An ROI is placed on the abnormality on an attenuation-corrected image, and the mean activity (MBq/mL) is measured. The decay-corrected activities are then used to compute the SUR with the following formula:

$$\text{SUR} = \frac{\text{mean ROI activity (MBq/mL)}}{\text{injected dose (MBq)/body weight (g)}}.$$

The use of lean body weight instead of total body weight has been advocated by some investigators. Correction for serum glucose has also been suggested. SUR values may change with time after FDG injection; thus, the time of acquisition after FDG injection must be standardized for the values to be useful (*13*).

Correlation between the PET images and a recent CT scan of the chest is needed for localization of small lesions that are near the chest wall or mediastinum. Image registration and image fusion have been used for combining anatomic information from CT scans and metabolic information from PET images (*14*). Methods for registration of CT and PET body images are becoming more readily available.

SOLITARY PULMONARY NODULES

Solitary pulmonary nodules are usually identified on routine chest radiographs that are obtained as part of preoperative evaluations or routine physical examinations. Solitary pulmonary nodules are identified in approximately 130,000 patients each year in the U.S. (*15*). Further radiographic evaluation is often performed with chest CT. If the nodule can be demonstrated to have a low likelihood of malignancy, serial plain radiographs are obtained to demonstrate that it is not enlarging. If the nodule is stable in size for 2 y or longer, it is likely benign. If the nodule is not definitely benign by its characteristics on a CT scan (*16,17*), then further evaluation is required.

The usefulness of FDG PET in characterizing pulmonary nodules and opacities as benign or malignant has been demonstrated by multiple studies (*11,12,14,18–36*). The reported sensitivity and specificity of FDG PET in differentiating benign lesions from malignant lesions have been uniformly high. The ranges in sensitivity, specificity and accuracy are 82%–100%, 75%–100% and 79%–94%, respectively. In a study of 81 patients for whom FDG PET scans were obtained for evaluations of indeterminate focal pulmonary opacities at our institution, Duhaylongsod et al. (*29*) noted that the mean SUR of malignant lesions (5.9 ± 2.7) was significantly different from the mean SUR of benign lesions (2.0 ± 1.7). Using an SUR of 2.5 as the cutoff value, the sensitivity was 100%, and the specificity was 79%. There was no correlation between lesion diameter and FDG uptake

as measured by the SUR. However, a significant correlation was found between the SUR and lesion doubling time (*36*).

In a prospective multicenter study of 89 patients who underwent evaluations of indeterminate solitary pulmonary nodules, FDG PET had a sensitivity of 92% and a specificity of 90% using the SUR data (*34*). Visual analysis of the images demonstrated a sensitivity of 98% and a specificity of 69%, and these results were not significantly different from the results using the SUR data. When the data were evaluated by separating the nodules into those between 0.7 and 1.5 cm in diameter and comparing them with those >1.5 cm in diameter, the sensitivity and the specificity were not statistically significantly different. Data are not available concerning the accuracy of detecting nodules <0.7 cm in diameter. Because of scanner resolution and nodule motion during the acquisition, accurate detection of nodules <0.7 cm in diameter is unlikely (*37*).

False-negative FDG PET scans have been reported to occur with primary pulmonary carcinoid tumors and with bronchoalveolar cell cancers (*38,39*). Six of seven carcinoid tumors had SURs <2.5 (*38*). Typical carcinoid tumors are slow growing and demonstrate minimal mitotic activity, factors that might result in less FDG accumulation than in NSCLC. Of seven bronchoalveolar lung carcinomas, four were considered negative by FDG PET images (*39*). The authors noted that these cancers have less proliferative potential and longer mean doubling times than for other NSCLC. A correlation was found between the amount of FDG accumulation and the degree of cell differentiation in adenocarcinomas of the lung.

Some active infectious or inflammatory lesions may have significant uptake of FDG. Tuberculous pneumonia, cryptococcosis, histoplasmosis, aspergillosis and other infections may have substantial FDG accumulation and SUR values in the abnormal range. However, most chronic or indolent inflammatory processes and most acute infectious processes do not have significant FDG accumulation. For this reason, the specificity of PET in the evaluation of focal pulmonary opacities remains high.

A recent study documented a relationship between prognosis and the amount of FDG uptake in nodules of patients with lung cancer (*40*). In 155 patients who had a new diagnosis of NSCLC and for whom FDG PET scans were obtained, the SUR value calculated from the primary lesion was correlated with clinical information to determine the prognostic significance of the PET scan result. Of the 118 patients with SUR values <10, a median survival of 24.6 mo was found, whereas the 37 patients with SUR values >10 had a statistically significant shorter median survival of 11.4 mo. Multivariate analysis demonstrated that the results of the PET scan provided prognostic information independent of other clinical and image findings.

STAGING

Because the mediastinum is the most common site for metastases, staging of lung cancer requires accurate evaluation of mediastinal nodes. Staging of the mediastinum is most reliably performed by mediastinoscopy; anatomic imaging studies are also used and complement other techniques. Adenopathy as defined by CT is both insensitive and nonspecific for malignancy. Staging of NSCLC using CT and MRI is reported to have a sensitivity of 52% and 48% and a specificity of 69% and 64%, respectively (*41*). Because the criterion used for diagnosis of mediastinal node disease is size dependent, the low accuracy of anatomic imaging is not surprising. Investigators have shown that mediastinal nodes harboring malignancy can be detected accurately by FDG PET and that FDG PET is more accurate than CT (*14,21,25,42–52*). The ranges in sensitivity, specificity and accuracy are 66%–100%, 81%–100% and 80%–100%, respectively. The accuracy of PET is better than that of CT in every study.

NSCLC frequently metastasizes to the adrenal glands. Although some reports have noted that in up to 60% of patients with NSCLC adrenal metastases will also develop during the course of the disease (*53*), adrenal masses at the time of initial presentation are more likely to be benign. In a study by Erasmus et al. (*54*), of 33 adrenal masses in 27 patients with NSCLC, 23 were demonstrated to be metastatic disease. PET had a 100% sensitivity and an 80% specificity in their study of CT-detected adrenal lesions between 1 and 9 cm in diameter.

Whole-body imaging is used to stage NSCLC. In a prospective study of 109 patients, the accuracy of whole-body PET was compared with that of conventional imaging (*55*). The sensitivity of FDG PET for the detection of distant metastases was 100%, with a specificity of 94% and an accuracy of 96%. FDG PET resulted in correctly modifying the stage (N and/or M) of the disease in 34% of patients (37/109) and changing the therapeutic strategy in more than 20% of patients. In a study of 99 patients for whom whole-body FDG PET scans were obtained, Valk et al. (*50*) identified previously unsuspected metastases in 11 patients. Normal PET findings were noted at sites of abnormality, suggesting metastatic disease in 19 patients.

DETECTION OF PERSISTENT OR RECURRENT DISEASE

In a prospective study of patients with lung cancer, FDG PET imaging was performed before radiotherapy in 20 patients and before and after radiotherapy in 12 patients (*56*). Using long-term follow-up, 4 patients who had complete response by PET had a local remission of disease. Eight patients had a partial response or no response to the FDG accumulation, and 4 of the 8 patients were alive 11–24 mo after therapy. In a study of 30 patients who had untreated lung cancer and for whom FDG scans were obtained before therapy, 20 patients also had PET scans obtained after treatment (*57*). Lesions with higher tumor-to-muscle ratios responded better to treatment than those with lower ratios. The decrease in FDG accumulation after therapy correlated with a partial response to therapy. The relapse rate was

higher in lesions with higher uptake ratios before and/or after therapy. The results of a pilot study of the use of FDG PET in monitoring response to chemotherapy in 13 patients with primary lung cancer and mediastinal metastases are promising (*58*).

Patz et al. (*59*) studied 43 patients on whom FDG PET scanning was performed between 4 and 182 mo after initial diagnosis and treatment of bronchogenic carcinoma. Thirty-five patients had recurrent or persistent cancer, documented by pathologic analysis in 25 patients or clinical and radiographic progression in 10 patients. The median SUR in the 35 patients who had recurrent or persistent cancer was 7.6 (range 1.9–18), whereas the median SUR in the patients who had fibrosis after therapy was 1.6 (range 0.6–2.4). Using an SUR value of >2.5 to indicate malignancy, FDG PET had a sensitivity of 97% and a specificity of 100% for the detection of persistent or recurrent disease. In another study of 39 lesions in 38 patients studied by FDG PET imaging after therapy for cancer, a sensitivity of 100% and a specificity of 62% were found (*60*).

COST-EFFECTIVENESS

Gambhir et al. (*61*) showed that a combined CT- and PET-based strategy is cost-effective in the staging of patients with NSCLC because it reduces the probability that a patient with unresectable disease will undergo an unnecessary attempt at curative surgery. On the basis of a decision-tree sensitivity analysis of FDG PET in staging and management of NSCLC, two decision strategies for potential surgical candidates were compared: (a) thoracic CT alone and (b) thoracic CT and thoracic PET. The study evaluated the expected costs and projected life expectancy. The CT and PET strategy showed savings of $1154 per patient without loss of life expectancy compared with the alternate strategy of CT alone. The major advantage of FDG PET is the cost savings that result from a patient with unresectable disease not undergoing an unnecessary surgery. This study calculated a savings of $98,000,000 per year, assuming 85,000 patients (on the basis of national cancer statistics) undergo the diagnostic algorithm each year. The cost savings and unchanged life expectancy are the result of improved staging of lung carcinoma before the decision for surgery. In a subsequent study using five decision strategies, a strategy that used PET after a negative CT study was shown to be a cost-effective alternative to the CT-only strategy (*62*).

FDG PET STUDY AVAILABILITY

Presently, there are approximately 60 sites in the U.S. that have dedicated PET scanners. Most of these sites have a cyclotron that produces ^{18}F, and the FDG is compounded and used on-site. Some centers with dedicated PET scanners and camera-based PET devices are obtaining FDG from regional distribution sites operated by a commercial vendor. These regional distribution sites are currently limited to 14 metropolitan areas, but the plan is to increase the availability of FDG by acquiring more sites for distributing FDG. The rapid increase in the number of PET devices and their clinical use will require more doses of FDG to be available for a greater number of imaging centers (*63*).

Camera-based PET devices are now available at many centers, and there are approximately three times the number of camera-based PET devices as there are dedicated PET scanners in the U.S. The number of camera-based PET scanners is increasing rapidly. These devices can be used for both general nuclear medicine studies and PET imaging. The performance of camera-based PET devices has improved dramatically since their introduction (*64*). The use of thicker crystals has improved the sensitivity of detecting annihilation radiation without affecting ^{99m}Tc radiopharmaceutical image quality. New iterative reconstruction algorithms are being used, and these algorithms provide better image quality than the filtered backprojection algorithms. Attenuation correction is available and improves the detection of small and deep-seated lesions.

Camera-based PET studies are performed using a 20- to 30-min acquisition that is started 30–60 min after the intravenous administration of 129.5–185 MBq (3.5–5.0 mCi) FDG. A phantom study demonstrated that pulmonary nodules that are 1.0 cm in diameter can be detected by attenuation-corrected camera-based PET scanning (*62*). In a study of 75 focal pulmonary lesions in 43 patients, nonattenuation-corrected camera-based PET detected 47 of 66 lesions that were abnormal on the dedicated PET scanner (*65*). Camera-based PET detected 90% of lesions >1.5 cm in diameter that were detected on the dedicated PET scanner. Thus, camera-based PET scans obtained without attenuation correction have a high concordance with dedicated PET scans of pulmonary lesions >1.5 cm in diameter.

REIMBURSEMENT

The Blue Cross/Blue Shield Technology Evaluation Center evaluated the literature supporting the use of PET in oncology in 1997. The panel of experts concluded that the data supported the use of FDG PET imaging in the evaluation of solitary pulmonary nodules and the staging of NSCLC (*63*). Blue Cross/Blue Shield has a policy of paying for PET scans for these indications. Many other third-party payers have similar policies. As of January 1, 1998, the Health Care Financing Administration (HCFA), which administers Medicare, has a policy to pay for FDG PET scans used in the evaluation of indeterminate solitary pulmonary nodules and the initial staging of lung cancer in patients with pathologically diagnosed NSCLC. Medicare is providing reimbursement for PET scans through the use of G-codes that incorporate information about prior studies and procedures such as an indeterminate CT scan and biopsy-proven NSCLC. The HCFA plans to use this information to track the use of PET and the procedures performed after the PET scan is obtained. For example, biopsies should be performed on few solitary pulmonary nodules after a PET scan has demonstrated a benign lesion. The Medicare policy requires

that the biopsy procedure be preapproved in this circumstance or it will not be reimbursed. The HCFA recently reviewed other indications of FDG PET scans, and these results should be forthcoming this year.

REFERENCES

1. Stanley K, Stjernsward J. Lung cancer. In: Hansen HH, ed. *Basic and Clinical Concepts of Lung Cancer*. Norwell, MA: Kluwer; 1989:4–11.
2. Kurihara M, Aoki K, Hisamichi S. *Cancer Mortality Statistics in the World: 1950–1985*. Nagoya, Japan: University of Nagoya Press; 1989.
3. Magrath I, Litvak J. Cancer in developing countries: opportunity and challenge. *J Natl Cancer Inst.* 1993;85:862–873.
4. Boring CC, Squires TS, Tung T. Cancer statistics: 1992. *CA Cancer J Clin.* 1992;42:19–43.
5. Mack MJ, Hazelrigg SR, Landreneau RJ, Acuft TE. Thoracoscopy for the diagnosis of the indeterminate solitary pulmonary nodule. *Ann Thorac Surg.* 1993;56:825–832.
6. Smith TAD. FDG uptake, tumour characteristics, and response to therapy: a review. *Nucl Med Commun.* 1998;19:97–105.
7. Ginsberg RS, Vokes E, Raben A. Non-small cell cancer of the lung. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*. Philadelphia, PA: Lippincott-Raven; 1997:858–911.
8. Lindholm P, Minn H, Leskinen-Kallio S, Bergman J, Ruotsalainen U, Joensuu H. Influence of the blood glucose concentration on FDG uptake in cancer: a PET study. *J Nucl Med.* 1993;34:1–6.
9. Hoh CK, Hawkins RA, Glaspy JA, et al. Cancer detection with whole-body positron emission tomography using fluorodeoxyglucose. *J Comput Assist Tomogr.* 1993;17:582–589.
10. Spritzer CE, Norconk JJ Jr, Sostman HD, Coleman RE. Detection of deep venous thrombosis by magnetic resonance imaging. *Chest.* 1993;104:54–60.
11. Lowe VJ, Hoffman JM, DeLong DM, et al. Semiquantitative and visual analysis of FDG-PET images in pulmonary abnormalities. *J Nucl Med.* 1994;35:1771–1776.
12. Patz EF, Lowe VJ, Hoffman JM, et al. Focal pulmonary abnormalities: evaluation with [^{18}F]fluorodeoxyglucose PET scanning. *Radiology.* 1993;188:487–490.
13. Lowe VJ, DeLong DM, Hoffman JM, Coleman RE. Optimum scanning protocol for FDG-PET evaluation of pulmonary malignancy. *J Nucl Med.* 1995;36:883–887.
14. Wahl RL, Quint LE, Greenough RL, et al. Staging of mediastinal non-small cell lung cancer with FDG PET, CT and fusion images: preliminary prospective evaluation. *Radiology.* 1994;191:371–377.
15. Lowe VJ, Coleman RE. Application of PET in oncology imaging. In: Sandler MP, Coleman RE, Wackers FJ Th, Patton JA, Gottschalk A, Hoffer PB, eds. *Diagnostic Nuclear Medicine*. 3rd ed. Baltimore, MD: Williams & Wilkins; 1995:1293–1308.
16. Mori K, Saitov Y, Tominaga K, et al. Small nodular lesions in the lung periphery: new approach to diagnosis with CT. *Radiology.* 1990;177:843–849.
17. Kuriyama K, Tateishi R, Doi O, et al. Prevalence of air bronchograms in small peripheral carcinomas of the lung on the thin-section CT: comparison with benign tumors. *AJR.* 1991;156:921–924.
18. Kubota K, Matsuzawa T, Fujiwara T, et al. Differential diagnosis of lung tumor with positron emission tomography: a prospective study. *J Nucl Med.* 1990;31:1927–1932.
19. Dehdashti F, Griffeth LK, McGuire AH, et al. FDG-PET evaluation of suspicious pulmonary and mediastinal masses [abstract]. *J Nucl Med.* 1992;33:961P.
20. Hunter GJ, Fischman AJ, Alpert NM, et al. Quantitative [^{18}F]FDG PET in the monitoring and management of response to lung cancer therapy [abstract]. *Radiology.* 1992;185:186P.
21. Strauss LG, Dimitrakopoulou AD, Haberkorn U, et al. PET follow-up studies to evaluate tumor perfusion and metabolism in patients with small cell carcinoma of the lung [abstract]. *Radiology.* 1992;185:139P.
22. Slosman DO, Spiliopoulos A, Couson F, et al. Satellite PET and lung cancer: a prospective study in surgical patients. *Nucl Med Commun.* 1993;14:955–961.
23. Knopp MV, Bischoff H, Ostertag H, et al. Clinical application of FDG-PET for staging of bronchogenic carcinoma [abstract]. *J Nucl Med.* 1993;34:21P.
24. Khonsary SA, Mandelkern MA, Brown CV, et al. PET-FDG scanning in pulmonary mass lesions [abstract]. *Clin Nucl Med.* 1993;18:922.
25. Berlangieri SU, Scott AM, Knight S, et al. Mediastinal lymph node staging in non-small-cell lung carcinoma: comparison of [^{18}F]-FDG positron emission tomography with surgical pathology [abstract]. *Eur J Nucl Med.* 1994;21:62S.
26. Weber W, Romer W, Ziegler S, et al. Clinical value of F-18-FDG PET in solitary pulmonary nodules [abstract]. *Eur J Nucl Med.* 1995;22:775.
27. Paulus P, Benoit TH, Bury TH, et al. Positron emission tomography with ^{18}F-fluoro-deoxyglucose in the assessment of solitary pulmonary nodules [abstract]. *Eur J Nucl Med.* 1995;22:775.
28. Baum RP, Rust M, Strassmann O, et al. Whole-body positron emission tomography with 2-[^{18}F]-fluorodeoxyglucose for preoperative staging of lung cancer: influence on patients' management [abstract]. *Eur J Nucl Med.* 1995;22:775.
29. Duhaylongsod FG, Lowe VJ, Patz EF, et al. Detection of primary and recurrent lung cancer by means of F-18 fluorodeoxyglucose positron emission tomography (FDG PET). *J Thorac Cardiovasc Surg.* 1995;110:130–139.
30. Hubner KF, Buonocore E, Singh SK, et al. Characterization of chest masses by FDG positron emission tomography. *Clin Nucl Med.* 1995;20:293–298.
31. Dewan NA, Reeb SD, Gupta NC, et al. PET-FDG imaging and transthoracic needle lung aspiration biopsy in evaluation of pulmonary lesions: a comparative risk-benefit analysis. *Chest.* 1995;108:441–446.
32. Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. *J Nucl Med.* 1996;37:943–948.
33. Lowe VJ, Duhaylongsod FG, Patz EF, et al. Pulmonary abnormalities and PET data analysis: a retrospective study. *Radiology.* 1997;202:435–439.
34. Lowe VJ, Fletcher JW, Gobar L, et al. Prospective investigation of PET in lung nodules. *J Clin Oncol.* 1998;16:1075–1084.
35. Conti PS, Lilien DL, Hawley K, et al. PET and [^{18}F]-FDG in oncology: a clinical update. *Nucl Med Biol.* 1996;23:717–735.
36. Duhaylongsod F, Lowe VJ, Patz EF, et al. Lung tumor growth correlates with glucose metabolism measured by FDG-PET. *Ann Thorac Surg.* 1995;60:1348–1352.
37. Coleman RE, Laymon CE, Turkington TG. FDG imaging of lung nodules: a phantom study comparing SPECT, camera-based PET and dedicated PET. *Radiology.* 1999;210:823–828.
38. Erasmus JJ, McAdams HP, Patz EF, Coleman RE, Ahuma V, Goodman PC. Evaluation of primary pulmonary carcinoid tumors using positron emission tomography with ^{18}F-fluorodeoxyglucose. *AJR.* 1998;170:1369–1373.
39. Higashi K, Ueda Y, Seki H, et al. Fluorine-18-FDG PET imaging is negative in bronchioloalveolar lung carcinoma. *J Nucl Med.* 1998;39:1016–1020.
40. Ahuja V, Coleman RE, Herndon J, Patz EF Jr. Prognostic significance of FDG-PET imaging in patients with non-small cell lung cancer. *Cancer.* 1998;83:918–924.
41. Webb WR, Gatsonis C, Zerhouni EA, et al. CT and MR imaging in staging non-small cell bronchogenic carcinoma: report of the Radiologic Diagnostic Oncology Group. *Radiology.* 1991;178:705–713.
42. Grimmel S, Storck M, Henrich M, et al. Diagnostic value of 18-F-FDG-PET in patients with lung cancer and lymph node metastases [abstract]. *Eur J Nucl Med.* 1993;20:819.
43. Buchpiguel CA, Tse K, Alavi A, et al. Use of quantitative FDG-PET whole-body imaging in staging lung cancer: a comparison with CT [abstract]. *Eur J Nucl Med.* 1994;21:61S.
44. Patz EF, Lowe VJ, Goodman PC, et al. Thoracic nodal staging with PET imaging with ^{18}FDG in patients with bronchogenic carcinoma. *Chest.* 1994;108:1617–1621.
45. Sasaki M, Ichiya Y, Kuwabara Y, et al. The usefulness of FDG-PET for the detection of mediastinal lymph node metastases in patients with non-small-cell lung cancer: a comparative study with x-ray CT [abstract]. *Eur J Nucl Med.* 1994;21:189S.
46. Scott WJ, Schwabe JL, Gupta NC, et al. Positron emission tomography of lung tumors and mediastinal lymph nodes using [^{18}F]fluorodeoxyglucose. *Ann Thorac Surg.* 1994;58:698–703.
47. Bury TH, Paulus P, Benoit TH, et al. Positron emission tomography versus computed tomography in the staging of mediastinal non-small-cell lung cancer [abstract]. *Eur J Nucl Med.* 1995;22:846.
48. Madar I, Hoh C, Figlin RA, et al. Cost-effective staging of non-small-cell lung carcinoma by whole-body PET FDG imaging [abstract]. *J Nucl Med.* 1995;36:57P.
49. Chin R Jr, Ward R, Keyes JW Jr, et al. Mediastinal staging of non-small-cell lung cancer with positron emission tomography. *Am J Respir Crit Care Med.* 1995;152:2090–2096.
50. Valk PE, Pounds TR, Hopkins DM, et al. Staging lung cancer by PET imaging. *Ann Thorac Surg.* 1995;60:1573–1582.
51. Sasaki M, Ichiya Y, Kuwabara Y, et al. The usefulness of positron emission tomography for the detection of mediastinal lymph node metastases in patients with non-small cell lung cancer: a comparative study with x-ray computed tomography. *Eur J Nucl Med.* 1996;23:741–747.
52. Sazon DAD, Santiago SM, Soo GW, et al. Fluorodeoxyglucose-positron emission tomography in the detection and staging of lung cancer. *Am J Respir Crit Care Med.* 1996;153:412–421.

53. Engleman RM, McNamara WL. Bronchogenic carcinoma: a statistical review of two hundred twenty-four autopsies. *J Thorac Surg*. 1954;27:227–239.
54. Erasmus JJ, Patz EF, McAdams HP, et al. Evaluation of adrenal masses in patients with bronchogenic carcinoma using FDG-PET imaging. *AJR Am J Roentgenol*. 1997;168:1357–1360.
55. Bury T, Dowlate A, Corhay JL, et al. Whole-body ^{18}FDG in the staging of non-small cell lung cancer. *Eur Respir J*. 1997;10:2529–2534.
56. Hebert M, Lowe V, Hoffman J, et al. Positron emission tomography in the pretreatment evaluation and follow-up of non-small cell lung cancer patients treated with radiotherapy. *Am J Clin Oncol*. 1996;19:416–421.
57. Ichija Y, Kuwabara Y, Sasaki M, et al. A clinical evaluation of FDG-PET to assess the response in radiation therapy for bronchogenic carcinoma. *Ann Nucl Med*. 1996;10:193–200.
58. Vansteenkiste J, Stoobants S, DeLyn P, et al. Prognostic significance of FDG-PET after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer (N2-NSCLC): analysis of 13 cases [abstract]. *Proc Am Soc Clin Oncol*. 1998;16:75.
59. Patz EF Jr, Lowe VJ, Hoffman JM, Baine SS, Harris LK, Goodman PC. Persistent or recurrent bronchogenic carcinoma: detection with PET and 2-[-18]-2-deoxy-D-glucose. *Radiology*. 1994;191:379–382.
60. Inoue T, Kim EE, Komaki R, et al. Detecting recurrent or residual lung cancer with FDG-PET. *J Nucl Med*. 1995;36:788–793.
61. Gambhir SS, Hoh CG, Phelps ME, et al. Decision tree sensitivity analysis for cost-effectiveness of FDG-PET in the staging and management of non-small cell lung carcinoma. *J Nucl Med*. 1996;37:1428–1436.
62. Scott WJ, Shepherd J, Gambhi SS. Cost-effectiveness of FDG-PET for staging non-small cell lung cancer: a decision analysis. *Ann Thorac Surg*. 1998;66:1876–1885.
63. Coleman RE, Tesar RD. Clinical PET: are we ready? *J Nucl Med*. 1997;38:8N–9N.
64. Coleman RE. Camera-based PET: the best is yet to come. *J Nucl Med*. 1997;38:1796–1797.
65. Delbeke D, Sandler MP, Al-Sugair A, et al. Comparison of dedicated and camera-based PET imaging of FDG in patients with focal pulmonary lesions [abstract]. *J Nucl Med* 1998;39:108P.