# *Lung Cancer Classification, Staging and Diagnosis*

**By:**

**Laurie E. Stallings, PharmD, BCNP**

# LUNG CANCER CLASSIFICATION,

# STAGING AND DIAGNOSIS

## STATEMENT OF OBJECTIVES

***Upon completion of this material, the reader should be able to:***

1. Discuss the histologic and clinical classification of bronchial carcinoma and how each type differs in its clinical features, metastatic spread, and response to therapy.
2. Outline the clinical presentation of lung cancer, with respect to local tumor effects, extrapulmonary signs and symptoms associated with metastatic involvement, and paraneoplastic syndromes.
3. Describe TNM staging and give patient/disease-related variables that affect therapeutic management options and prognosis.
4. Describe the mechanisms of action of each radiopharmaceutical used in the imaging of neoplastic lung disease.
5. List the advantages and disadvantages of using $^{18}$FDG PET vs. $^{99m}$TC-depreotide SPECT.
6. List the clinical indications for $^{18}$FDG PET
7. Discuss the clinical utility of these functional imaging agents and how they fit in the diagnostic algorithm of lung cancer.

## EPIDEMIOLOGY

Lung cancer is the leading cause of cancer mortality in both men and women in the United Sates, accounting for 28% of all cancer deaths.[1,2] It is estimated by the American Cancer Society that 164,100 new cases were diagnosed in the year 2000, representing no significant decrease in incidence, despite vigorous smoking cessation campaigns.[2,3] With approximately 156,900 deaths attributed in 2000 alone, lung cancer has been the leading cause of cancer death in men since the early 1950's, and surpassed breast cancer in 1987 as the leading cause of cancer deaths in women.[3,4] The mean survival time for untreated lung cancer is only six months.[5] The 5 year survival rates for patients diagnosed with lung cancer is only 14% for whites, 11% for blacks, and remains unchanged over the past 20 years.[(2,3)] Due in part to ineffective screening mechanisms, about 47% of patients will have advanced pulmonary neoplastic disease (stage IV) at the time of diagnosis.[6]

It is clear that the current approach of using modalities based on the detection of anatomical and morphological changes is insensitive for diagnosing bronchogenic cancer in its early and most treatable stages. Furthermore, invasive procedures for tissue sampling, such as bronchoscopy, percutaneous needle biopsy, thorascopy, and open lung biopsy, represent significant cost, in terms of patient morbidity and hospital stay. Since physiopathologic and biochemical changes occur before gross structural and anatomical changes, noninvasive functional imaging could detect changes earlier in the course of disease and, in selected patients, decrease morbidity associated with invasive procedures.

## ETIOLOGY AND PATHOPHYSIOLOGY

The pathogenesis of a neoplastic lesion begins with the exposure of pluripotent epithelial cells to carcinogens. Subsequently, chronic inflammation leads to genetic and cytologic mutations, with the activation of cellular oncogenes and stimulation of cellular proliferation by growth factors.[7]

Cigarette smoking is responsible for >90% of bronchogenic cancers.[2] A dose response relationship between smoking pack-years and cancer risk has been established, with the curve steepest for small cell lung cancer (SCLC) and least steep for adenocarcinoma.[7] Smoking cessation decreases the risk, but a long latency period exists between smoking cessation and risk normalization. It requires about 5 years of non-smoking before any significant reduction in risk is realized, and 25 years before the cancer risk equals that of a lifelong nonsmoker.[8]

Occupational and environmental carcinogens result in pulmonary neoplasms in about 15% of men and 5% of the women exposed to pulmonary toxins.[7] The list includes: asbestos, chloroethyl methyl ether, heavy metals such as nickel and chromium, arsenic (glass, pesticides, paints), aromatic hydrocarbons, radon, and ionizing radiation.[7]

The fact that only about 10% of heavy smokers die of lung cancer suggests a possible genetic component to the pathogenesis of lung cancer.[1] There may be a genetic predisposition for the activation of certain enzymes by smoking to convert hydrocarbons to carcinogens.

Dietary factors may also have a role in the development of cancer. Studies show a relationship between the increased intake of fresh vegetables and a lower cancer risk, possibly linked to the chemoprotective effects of beta-carotene.[1]

## HISTOLOGIC CLASSIFICATION

### Major Cell Types

As classified by the World Health Organization (WHO), four major cell types account for more than 90% of primary lung

tumors[9]: squamous cell carcinoma, adenocarcinoma, large cell, and small cell carcinoma. This histologic classification is necessary because of differences in natural history, radiologic features, clinical presentation, and response to treatment of the different cell types. Based on differences in management strategy and overall prognosis, a clinical distinction is made between small cell lung cancer (SCLC; ~20% of cases) and non-small cell lung cancer (NSCLC; 80% of cases), which encompasses squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

Squamous Cell Carcinoma

Squamous cell carcinoma accounts for 25 - 30% of all lung cancer, with an increased incidence in smokers and males.[10] This pathologic cell type usually arises from the epithelium of larger, more proximal bronchi and commonly extends into, and obstructs, the bronchial lumen. Light microscopy reveals keratinization and "pearls" (flattened cells surrounding a central core of keratin) and intercellular bridges.[1] Squamous cell carcinoma is the type least likely to metastasize (54% compared to 82% for adenocarcinoma, 86% for large cell carcinoma),[1] although it can metastasize via lymphatic spread to hilar and mediastinal lymph nodes, liver, adrenal glands, kidney, bone and the gastrointestinal tract.[7] In addition, brain metastases are found in greater than 50% of patients on post mortem examination.[1] Hypercalcemia is common secondary to the secretion of a parathyroid hormone-like compound, and the tumor may also cause secretion of growth hormone, corticotropin, calcitonin, and follicle stimulating hormone.

Adenocarcinoma

Adenocarcinoma is the most common cell type seen in the United States (30 – 35%), with a higher incidence seen in women, and is the most frequently occurring cell type in non-smokers.[4] Lesions usually arise in the peripheral lung and follow a glandular and papillary pattern. Spreading through the bloodstream and lymphatics, there is an increased likelihood of early metastasis, even before diagnosis.[7] Organs targeted for metastatic spread include the contralateral lung, liver, bone, adrenal glands, kidneys, and the central nervous system. Adenocarcinomas and large cell carcinomas are the cell types most likely to metastasize to the brain.[1]

Large Cell Carcinoma

Large cell carcinoma (about 14%-19% of all lung cancers) is NSCLC, which is not classified as either adenocarcinoma or squamous cell carcinoma by light microscopy. It is comprised of two major subtypes: giant cell and clear cell.[1] This tumor type usually presents as a large, bulky, undifferentiated lesion found in the lung periphery and generally follows the same presentation and metastatic patterns as adenocarcinomas.

Small Cell Carcinoma

Small cell lung cancer accounts for only about 20-25% of all lung cancers,[11] but has the most aggressive clinical course of all pulmonary tumors. These neoplastic cells have round to oval nuclei with very little cytoplasm. Characteristic electron microscope features include the presence of neurosecretory granules and neurofilaments. Enzymes are released that decarboxylate amino acids, resulting in biologically active amines and hormones (i.e., ADH, ACTH).[11] Seventy percent of SCLC is diagnosed from a large central mass in the lung,[1,4] with extensive mediastinal lymph node involvement and mucosal and submucosal invasion. SCLC is characterized by rapid growth and a high likelihood of early hematogenous metastases by the time of diagnosis. Likely metastatic

target organs include lymph nodes, contralateral lung, liver, adrenal glands, other endocrine organs, bone, bone marrow, and the central nervous system. Bone marrow metastases are found in about 15%-25% of patients and central nervous system metastases in approximately 10% of patients at the time of diagnosis.[1]

The median survival time for untreated SCLC is a mere 2 to 4 months, with the overall 5-year survival rate in treated cases 5 -10%.[12-15]

Because of the propensity for wide dissemination at diagnosis, localized forms of treatment, such as surgery and radiation, are often not effective for long-term survival.[12] SCLC is much more responsive to chemotherapy, but even high response rates do not translate into high levels of long-term survival[13,16] because, even when proper treatment results in complete remission, most patients eventually relapse and die.

In a small subset of SCLC patients (5%-10%), surgical resection remains a viable option. If histology has been determined bronchoscopically and the mass is limited to lung parenchyma without evidence of distant metastases, surgery with adjuvant chemotherapy (because of high risk of the development of metastases following surgery) is recommended.[11]

**Metastatic Tumors of the Lung**

Metastatic tumors from a primary tumor elsewhere in the body are more common than primary tumors of the lung.[17] Approximately 33% of patients with malignant cancer will develop lung metastases, via direct contact or hematogenous or lymphatic spread, at some time during the course of the disease.[17] Some cancers, such as renal cell carcinoma, choriocarcinoma, melanoma, Wilm's tumor, and osteosarcoma, are associated with a high incidence of metastases to the lung at the time of diagnosis.[17]

**CLINICAL PRESENTATION**

Clinical manifestations of bronchogenic carcinoma depend on the location and extent of the lesion. Large central tumors will have earlier signs and symptoms of disease, while peripheral lesions may be asymptomatic until they invade either the pleura or chest wall, or metastasize to distant organs.[7] Based on location and extent of disease, the clinical presentation is classified by three descriptive categories: (1) local signs and symptoms associated with the primary tumor and mediastinal spread; (2) extrapulmonary signs and symptoms associated with metastatic spread; and (3) endocrinologic signs and symptoms of paraneoplastic syndromes. See Table 1.

In patients with localized disease, the most common symptoms are related to obstruction of major airways, infiltration of lung parenchyma, or invasion of surrounding structures, including the chest wall, major blood vessels, or viscera.

Airway obstruction is often associated with dyspnea, wheezing, cough (or change in cough in smokers), hemoptysis, and may precipitate pneumonia or atelectasis, secondary to partial or complete bronchial obstruction.[7,8] Symptoms related to mediastinal spread depend upon the structure that is invaded. A pleural effusion can result from contiguous spread of the tumor into the pleural surface; chest pain may be due to chest wall invasion by peripheral lung cancer. Pancoast's tumors cause shoulder and arm pain with generalized weakness secondary to brachial plexus compression as the apical tumor infiltrates the brachial plexus, neighboring ribs, or vertebrae.[8] Horner's syndrome is usually precipitated by cervical sympathetic chain involvement from an apical tumor, producing ptosis, miosis, and ipsilateral facial anhidrosis.[1] In the superior vena cava syndrome, tumor obstruction of venous drainage leads to dilation of veins in the chest, neck and face and subsequent edema in those areas.[7]

**Table 1 : Common Signs and Symptoms of Lung Cancer**

**Local signs and symptoms associated with primary tumor or regional spread within the thorax**

- Cough
- Hemoptysis
- Dyspnea
- Rust-streaked or purulent sputum
- Chest, shoulder, or arm pain
- Wheeze and stridor
- Superior vena caval obstruction
- Pleural effusion or pneumonitis
- Dysphagia (secondary to esophageal compression)
- Hoarseness (secondary to laryngeal nerve paralysis)
- Horner's syndrome
- Phrenic nerve paralysis
- Pericardial effusion/tamponade
- Tracheal obstruction
- Pancoast's syndrome

**Extrapulmonary signs and symptoms associated with metastatic involvement**

- Bone pain and/or pathologic fractures
- Liver dysfunction
- Neurologic deficits
- Spinal cord compression
- Adrenal insufficiency

**Paraneoplastic syndromes**

- Weight loss
- ACTH secretion/Cushing's syndrome
- PTH-like hormone secretion/Hypercalcemia
- Syndrome of inappropriate antidiuretic hormone (SIADH)
- Pulmonary hypertrophic osteoarthropathy
- Clubbing
- Anemia
- Eaton-Lambert myasthenic syndrome
- ADH secretion, leading to water retention and hyponatremia
- Vascular and hematologic manifestations (anemia, thrombophlebitis, DIC, granulocytosis, polycythemia)
- Peripheral neuropathies
- Dementia
- Gynecomastia
- Hypoglycemia (insulin-like secretion)
- Hyperglycemia
- Hyperpigmentation (MSH)
- Thyrotoxicosis

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Adapted from Finley, RS. Lung Cancer. In: DiPiro JT, Talbert RL, Hayes PE, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach.* New York: Elsevier Science; 1992:1946-1957. Used with permission.

**Table 2 : TNM Descriptors**

**Primary tumor (T)**

| | |
|---|---|
| TX | Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ* |
| T1 | Tumor ≤3cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus* (*i.e.*, not in the main bronchus) |
| T2 | Tumor without any of the following features of size or extent:<br>- >3cm in greatest dimension<br>- Involves main bronchus, ≥2cm distal to the carina<br>- Invades the visceral pleura<br>- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung. |
| T3 | Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus <2cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung |
| T4 | Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with a malignant pleural or pericardial effusion, ** or with satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung |

**Regional lymph nodes (N)**

| | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumor |
| N2 | Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s) |
| N3 | Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) |

**Distant metastasis (M)**

| | |
|---|---|
| MX | Presence of distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis present*** |

*The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

**Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid show no tumor. In these cases, the fluid is nonbloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient's disease should be staged T1, T2, or T3. Pericardial effusion is classified according to the same rules.

*** Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung also are classified M1.

Adapted from Mountain CF: Revisions in the International System for Staging Lung Cancer. *Chest*. 1997;111:1710-1717. Used with permission.

**Table 3 : Stage Grouping – TNM Subsets***

| Stage | TNM Subset |
|---|---|
| 0 | Carcinoma in situ |
| IA | T1N0M0 |
| IB | T2N0M0 |
| IIA | T1N1M0 |
| IIB | T2N1M0 |
| | T3N1M0 |
| IIIA | T3N1M0 |
| | T1N2M0 |
| | T2N2M0 |
| | T3N2M0 |
| IIIB | T4N0M0 |
| | T4N1M0 |
| | T4N2M0 |
| | T1N3M0 |
| | T2N3M0 |
| | T3N3M0 |
| | T4N3M0 |
| IV | Any T, Any N, M1 |

*Staging is not relevant for occult carcinoma, designated TXN0M0.

Adapted from Mountain CF: Revisions in the International System for Staging Lung Cancer. *Chest.* 1997;111:1710-1717. Used with permission.

Metastatic involvement produces signs and symptoms that are determined by the affected organ: bone pain, fractures, seizures, increased liver function enzymes, and neuromyopathies are common.

Paraneoplastic syndromes are metabolic, endocrinologic and neuromuscular disturbances that are unrelated to the primary tumor.[7] Because of the biologically active peptide hormones that are produced as a result of overexpressed somatostatin type receptors in SCLC,[18-22] paraneoplastic syndromes are more common in SCLC than in NSCLC. Although the syndrome of inappropriate antidiuretic hormone (SIADH) secretion is the most common paraneoplastic phenomenon in SCLC, only about 5%-10% of patients actually present with SIADH, another 40%-50% have subclinical abnormalities.[1] Twenty-five percent of patients with SCLC will have an elevated ACTH, though only 3%-7% develop Cushing's syndrome.[1]

## STAGING OF LUNG CANCER

### NSCLC

Non-small cell lung cancer is staged in a methodical and detailed manner to reflect progression of disease, allow appropriate patient management, predict prognosis, and allow comparisons of treatment results. The tumor/node/metastasis (TNM) staging system is used, and has been recently revised.[23] See Table 2.

TNM Staging

Accurate staging requires assessment of the three major indices of disease progression: tumor size, the extent of lymph node involvement, and the presence or absence of distant metastases. Invasion of the mediastinum can be a treatment-limiting factor. Therefore, assessment of mediastinal lymph nodes and invasion of regional vasculature, chest wall, or other mediastinal structures is essential.

Stage groupings represent subsets of patients with similar treatment options and survival expectations.[23] See Table 3.

In Stage I, the tumor is confined to the lung, with neither lymph node involvement nor the presence of distant metastases. Stage II is based on both tumor size and nodal status, with tumor infiltration into the ipsilateral hilum and/or peribronchial lymph nodes. Group IIB includes patients with larger tumors and negative node involvement (T3N0). The T3N0 patients were moved from stage IIIA to IIB, reflecting increased survival probability over group III.

Stage IIIA contains patients with large tumors and either ipsilateral or contralateral lymph node involvement. Stage IIIB is a heterogeneous group, including any size tumor; ipsilateral, contralateral, or mediastinal lymph node involvement; and tumor invasion of the mediastinum. The presence of a pleural effusion constitutes a T4 tumor (stage IIIB), since 90%-95% of pleural effusions in lung cancer patients are caused by tumor invasion of the pleura.[24]

Stage IV is based on the presence of distant metastases, regardless of tumor size or degree of lymph node involvement, and reflects the worst prognosis of the four groups.

The staging system is also based on a clinical and pathological distinction.[25] Clinical staging focuses on non-invasive or minimally invasive tests such as physical examination, laboratory tests, and radiologic and nuclear medicine studies.

Pathological staging is based on tissue biopsy and operative findings during bronchoscopy, mediastinoscopy, or anterior mediastinotomy.

Prognosis

The most important prognostic factor is the stage of disease, followed by post-treatment performance status and weight loss. Performance status is determined using two different scales: the ECOG (Eastern Cooperative Oncology Group) and the Karnofsky Scale. These rate the patient's ability to perform activities of daily living. See Table 4.

Patients that remain ambulatory (ECOG value 0 – 2, Karnofsky >50%) and experience a weight loss of ≤5% have a much better prognosis and overall survival rate than moribund or cachectic patients.[26-29] Poor performance status is also associated with a higher risk for treatment-related toxicity.[29]

Other decisive prognostic indicators include histologic tumor type, number and location of metastatic lesions, sex (prognosis worse for males), tumor grading/doubling time, mutations of p53, and presence of *ras* oncogenes.[6,26]

Treatment Options Based on Staging

Generally, stage I (N0 – no lymph node involvement) and stage II (N1 – spread to ipsilateral bronchopulmonary or hilar lymph nodes) are candidates for surgical resection. Stage IIIB patients (spread to contralateral lymph nodes) and stage IV (metastatic disease) have unresectable carcinoma.[30] Surgical management of stage IIIA (N2 – involvement of ipsilateral mediastinal lymph nodes) is controversial. Twenty percent of patients in this category are designated as having "minimal" disease and are considered surgically resectable.[30] The rest have "advanced" disease, with little or no potential for curative surgery. Therefore, the challenge is to correctly identify patients with

**Table 4: Performance Status Criteria**

| ECOG Performance Status Scale* | | Karnofsky Performance Scale | |
|---|---|---|---|
| **Grade** | **Description** | **Percent** | **Description** |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

*Adapted from Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.

N0, N1, and minimal N2 for surgical excision, and avoid unnecessary surgery in patients with advanced N2 and N3 disease.

**SCLC**

Since occult or overt metastatic disease is present in most small cell lung cancer patients at the time of diagnosis, minimal differences in tumor size and lymph node involvement do not affect survival rates. Hence, the TNM system is not used. SCLC is usually described as limited (M0) or extensive (M1). Limited disease (40% of SCLC patients at diagnosis) is defined as being limited to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes,[31] and excludes patients with pleural effusions.[11] The median survival rate, given current therapy, is 16 to 24 months for these patients.[32,33,34] A small portion of the patients are considered surgically resectable, with an associated improvement in prognosis. Patients with disease which spreads beyond the supraclavicular lymph nodes (60%) have extensive disease and a predicted survival of 6 to 12 months.[31] Patients presenting with CNS or liver metastases at diagnosis have a significantly worse prognosis.[31]

Because of the recalcitrant nature of this disease, staging procedures for SCLC include computed tomography (CT)/magnetic resonance imaging (MRI) of chest and abdomen, bone marrow biopsy (if lactic dehydrogenase is high), a brain CT, and a radionuclide bone scan.[16,31]

**DIAGNOSIS OF LUNG CANCER**

Screening and Patient Evaluation

Screening trials, using sputum cytology, have failed to show a survival advantage.[8] Recent spiral CT studies have documented the ability of low-dose spiral CT to detect cancer at an early stage.[8] Although many institutions are not routinely screening high risk patients with chest x-ray (CXR) or CT, a peripheral nodule is often first detected by CXR in asymptomatic patients.[7]

Work-up for suspected bronchial cancer would begin with a thorough history and physical to identify risk factors (smoking, occupational exposure, etc.), signs and symptoms of a primary tumor, extrapulmonary signs and symptoms of metastases, and paraneoplastic syndromes. Essential laboratory tests include CBC (anemia is indicative of a poor prognosis), urinalysis, LFTs, alkaline phosphatase and serum calcium. In symptomatic patients, a CXR may show bronchial narrowing, parenchymal infiltration, gross lymph node enlargement, atelectasis, tumor-related pleural effusion, and metastases within the thorax.[7] Stability of an abnormality over a period of $\geq$2 years suggests a benign lesion, therefore reviewing past CXRs may assist in the differential diagnosis of benign vs. malignant lesions.[35] Also, calcification indicates that a lesion is likely to be benign.[35] CT further elucidates suspicious masses found on CXR, and assesses tumor size and location, and extension to mediastinal structures, such as lymph nodes, thymus, bronchi, pericardium, pleura, and thoracic vasculature.

Pathological confirmation is obtained from sputum cytology and tumor biopsy by fiberoptic bronchoscopy, percutaneous needle biopsy, or open lung biopsy. Bronchoscopy is able to detect central tumors of the major bronchi and their primary divisions, but provides limited information on peripheral lesions. Thoracotomy is required for washing, brushing, and biopsy of more peripheral lesions.[1,7] Mediastinoscopy may be used to evaluate mediastinal and hilar lymph nodes.

In histopathologically confirmed malignant lesions, the presence of distant metastases can be determined with CT of the brain, abdominal ultrasound, skeletal scintigraphy, etc. Radionuclide bone scans have a high sensitivity but a low specificity for diagnosing neoplastic disease.[17]

Functional diagnosis is also included in the patient work-up to determine if the

patient can withstand surgery. The cardiopulmonary reserve of the patient is assessed with measures such as lung function testing, ABGs, EKG, and multi-gated acquisition (MUGA) cardiac ejection fraction, etc. Quantification of the patient's ventilation/perfusion deficit will identify high surgical risk patients who are at risk for postoperative morbidity and mortality, and estimate residual pulmonary reserve post lobectomy/pneumonectomy.

**Problematic Diagnosis of a Single Pulmonary Nodule**

Detection of lung cancer often occurs at the stage of the single pulmonary nodule (SPN). The SPN can be of any primary histologic type or a metastasis from a primary tumor elsewhere. By definition, an SPN is "a single lesion, regardless of size, surrounded by lung parenchyma on at least 2/3 of its circumference, not touching the hilum or mediastinum, and without associated atelectasis or pleural effusion."[7] The differential diagnosis for an SPN includes neoplasms, infections (e.g., *Coccidioides immitis, Histoplasma capsulatum*), and collagen vascular disease (e.g., Wegener's granulomatosis). Approximately 130,000 SPNs are discovered annually in the United States,[35] with about 75% of them detected in CXRs obtained for diagnoses other than lung cancer.[5] The incidence of developing a malignant SPN increases with age, such that greater than 50% of SPNs will be malignant in the age group over 50 years.[1] Because only 20% to 25% of SPN cases are symptomatic, an average of 7 months lapses before a definitive diagnosis is made.[5] Diagnosis of smaller nodules and those from younger, healthier patients may take even longer. Only a fraction of SPN lesions (28%-39%)[36,37] are malignant, but 90% of these malignant lesions are bronchogenic carcinoma.[7]

Conversely, 60% of SPNs are benign. Before the routine use of CT, 60% of surgically excised SPNs were histologically confirmed to be benign.[35] Although reduced to 20%-40% by CT,[(35)] conventional anatomic techniques, such as CT and CXR lack specificity and result in a high number of indeterminant cases.[38-42] This poses a diagnostic dilemma and forces the clinician to go to more invasive procedures to obtain the diagnosis. Invasive procedures may not have high sensitivity/specificity, and are associated with inherent problems of their use.

Sputum cytology gives a diagnostic yield of only 31%, with limited information on the location and extent of disease.[43] Fiberoptic bronchoscopy, including bronchial washing and brushing, has a sensitivity of about 65%[44,45] for malignancy in SPN lesions >2cm and 15% in smaller lesions.[46] Adding transbronchoscopy increases the sensitivity to 79%.[44,47]

Transthoracic fine needle aspiration (TTNA) has a sensitivity of 94%-98%,[48,49] and a specificity of 91%-96%, although some investigators have found sensitivity and specificity to be lower.[50] It is also associated with significant morbidity: 18%-26% of patients developed pneumothorax, with 10%-15% of these requiring chest tube placement.[49,51]

Winning, et al[52] found that in 181 patients with SPN, 40% of TTNA biopsies resulted in an indeterminant diagnosis; 40% of these lesions were later determined by histology to be malignant. Only 16% of patients with benign lesions were definitely negative on TTNA.

Thorascopic lung biopsy yields a definitive diagnosis, but in a recent study, over 50% of radiographically indeterminant SPNs resected by thoracoscopy were benign.[53] Therefore, potentially half of the patients in this study underwent an unnecessary invasive procedure.

Referring all indeterminant cases to biopsy results in increased morbidity and cost to both the patient and the healthcare system. Highly sensitive and specific noninvasive procedures, such as radionuclide functional imaging, could select the subset of patients most likely to benefit from biopsy, both reducing the number of biopsies and obtaining a higher yield of those performed.

**Positron Emission Tomography (PET) Using $^{18}$F-fluorodeoxyglucose ([$^{18}$F]FDG)**

Mechanism of Action

Cancer cells are highly metabolically active. Rapid cell proliferation increases the demand for substrates required for the synthesis of cellular components and energy to fuel these chemical processes. Protein and nucleic acid syntheses are enhanced in tumor cells, with increased amino acid transport.[54,55] Tumor cells have lower levels of glucose-6-phosphatase and increased hexokinase,[54,56] promoting glycolysis. Fluorodeoxyglucose (FDG) is a glucose analog labeled with the positron emitter fluorine-18. Once phosphorylated, $^{18}$FDG-6-phosphate is trapped within the tumor cell and cannot proceed through glycolytic or glyconeogenic pathways.[30] Thus, it can be used as a metabolic marker of malignant tissue.

Box 1 provides an example of an FDG imaging procedure, although it should be noted that protocols will vary from one institution to another.

Imaging with FDG PET

Patient preparation for FDG whole-body PET scanning consists of a 4-hour fasting period before the scan, hydration prior to FDG administration, post-injection

**Box 1:**

**Procedure for FDG Whole-Body PET Scanning**

- Patient Preparation
  - Fasting period of 12 hours (at least 4 – 6 hours), check blood glucose level *before* FDG administration (blood glucose, if possible, 90 mg/dl)
  - Non-caloric beverages (mineral water) are permitted
  - Injection of 300 – 500 MBq $^{18}$F-FDG (2D technique, full ring scanner)
  - Rest period (physical immobility) of at least 45 – 60 minutes (optimal: 90 – 120 minutes) before emission scan
  - Hydration (0.75 – 1 liter of mineral water, beginning approximately 15 minutes before the FDG injection)
  - I.V. administration of a diuretic (furosemide: 20 – 40mg), approximately 20 minutes after FDG injection)

- Imaging Technique
  - Transmission scan (5 – 10 minutes, approximately 50% of the time required for the emission scan) in the form of a "hot transmission scan," if necessary also after the emission scan
  - Emission scan: 8 – 15 minutes per bed position (calculated by elapsed time post-injection) from mid-thigh to base of skull

- Options
  - Transmission scan before the FDG injection ("cold transmission scan"), possibly with subsequent repositioning of the patient
  - Separate image of the brain (beginning approximately 30 – 45 minutes post-injection)
  - Reduced $^{18}$F activity for 3D scanning of coincidence cameras

Adapted from Baum RP, Presselt N, Bonnet R. Pulmonary nodules and non-small-cell bronchial carcinoma. In: Ruhlman J, Oehr P, Biersack HJ, eds. *PET in Oncology: Basics and Clinical Applications*. Heidelberg: Springer-Verlag. 1999:107. (Permission pending.)

diuresis, and patient immobility for the duration of the scan.

Patient fasting is necessary to decrease the competitive inhibition of FDG uptake by serum glucose. In patients with a history of glucose intolerance, serum glucose is monitored and FDG given only if serum glucose is less than 200 mg/dl.[57] Co-administration of FDG and insulin to a patient with high serum glucose results in increased uptake in the heart, liver, and skeletal muscle, rather than the tumor.[57] Although the effect of diabetes on tumor FDG accumulation has not been extensively studied, it does appear that acute serum hyperglycemia may result in decreased FDG accumulation in the tumor.[58] Dosing at 0.145 uCi/kg to a maximum of 20 mCi is appropriate for a dedicated PET scanner, but sodium iodide-based PET scanners cannot acquire data accurately at high count rates, requiring either lower doses of 5mCi to 7 mCi or a delay before scanning.[57]

Image Interpretation

FDG PET images can be interpreted qualitatively, quantitatively, or semi-quantitatively. In a qualitative interpretation, the physician uses visual inspection to compare the abnormal area [region of interest (ROI)] with background activity. Quantitative measures use absolute glucose values and are rarely used clinically. Semi-quantitative methods use attenuation-corrected images to generate a standard uptake value (SUV).

$$\text{SUV} = \frac{\text{mean ROI activity (mCi/ml)}}{\text{Injection dose (mCi)/body weight (g)}}$$

The SUV is an uptake value that is normalized for patient weight and imaging dose and is, therefore, more useful for comparison between patients. The SUV is time-dependent, hence activity at a standard time of 45 – 60 minutes post-injection is used.[57] Correction for serum glucose and lean body mass may improve accuracy. Some investigators use an SUV >2.5 as indicative of malignancy,[59] while others use the qualitative measure of FDG uptake greater than mediastinal uptake (in the absence of mediastinal disease).

PET Indications

FDG PET indications include: (1) accurately identifying malignancies in lesions found to be indeterminant from CT; (2) staging of the mediastinum and lymph node involvement; (3) detection of distal metastases; and (4) recurrence diagnoses and evaluation of response to treatment.

*Indication 1: SPN and Primary Tumor Detection.* The first well-documented application of FDG PET was the characterization of SPNs <3cm that were indeterminant from CT. FDG PET has a high sensitivity and specificity (near 100%)[59] for evaluating the metabolic activity of these lesions to distinguish between benign and malignant etiologies. See Table 5.

There is some controversy over the prognostic significance of the SUV. Several investigators[60-62] found a positive correlation between the level of tumor metabolic activity (i.e. SUV) and the probability of post-operative metastasis, adversely affecting survival rates. However, other findings suggest that, at best, the SUV is a useful adjunctive tool in diagnosis but has limited proven utility in predicting survival.[63-65]

Because increased glucose metabolism is also present in acute inflammatory/infectious lesions, false positive FDG PET studies have been documented in patients with tuberculosis histoplasmosis, Wegener's granulomatosis and sarcoidosis.[59,66-68]

False negative FDG PET studies occur into 3 specific settings: (1) tumors with low metabolic activity, such as carcinoid[69,70] and bronchioloalveolar cell carcinoma[71]; (2) small tumors <6mm[72]; and (3) acute hyperglycemic states.[73,74] The prospective investigations for PET (PIP) in lung cancer

**Table 5**
**Characterization of SPN and Detection of Primary Lung Carcinoma with PET**

| Author | Year | No. Patients | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|
| Rigo | 1997 | 109 | 98 | 89 | 90 | 89 |
| Dewan | 1993 | 30 | 95 | 80 | 94 | 80 |
| Scott | 1994 | 62 | 94 | 80 | 93 | 100 |
| Dewan | 1995 | 76 | 100 | 78 | 95 | 82 |
| Gupta | 1996 | 61 | 93 | 88 | | |
| ICP | 1993 | 237 | 96 | 90 | | |
| Lowe | 1998 | 98 | 92 | 90 | 86 | 92 |
| Lowe | 1997 | 197 | 96 | 77* | | |
| Guhlman | 1997 | 46 | 94 | 86 | | |
| Knight | 1996 | 48 | 100 | 63 | | |
| Gupta | 1992 | 20 | 100 | 100 | | |
| Patz | 1993 | 51 | 89 | 100 | | |
| Duhaylongsod | 1995 | 87 | 97 | 82 | | |
| Hubner | 1995 | 23 | 100 | 67 | | |
| Sazon | 1996 | 82 | 100 | 52 | | |

* Physicians discontinued utilizing biopsy to verify negative studies.

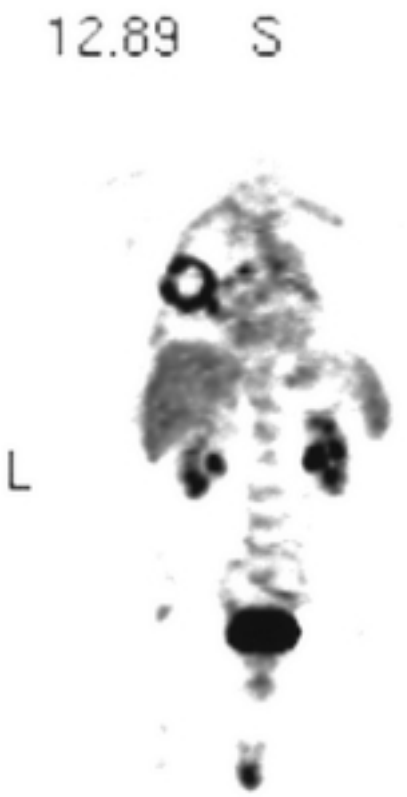


***Figure 1.*** Coronal image from whole-body $^{18}$FDG PET scan reveals a large right lung neoplasm with central necrosis (hence "donut" appearance). Small lymph nodes in hilum and mediastinum represent metastatic disease. Normal uptake is demonstrated in the liver, spleen, kidneys and bladder. Reprinted courtesy of Dr. Edward Coleman, Duke University, Durham, NC.

demonstrated a lower sensitivity (80%) for malignant tumors <1.5cm.[72]

FDG PET has a 90% to 95% positive predictive value,[8] which may be lower in areas such as the southeast which has a high prevalence of granulomatous disease. The negative predictive value is very high, such that if the lesion is >1cm and negative on FDG PET scan, then there is only a 5% chance of malignancy.[8] There may be a verification bias in some studies which report a lower specificity, since some physicians elect to forego biopsy in the event of a negative PET scan.[75]

A comparison of FDG and TTNA, a more invasive procedure, found the sensitivity/specificity of FDG versus TTNA to be 100%/78% and 81%/100%, respectively for the detection of indeterminate nodules.[76] If the sensitivity of TTNA were less than that obtained by FDG, malignancies would be missed. Conversely, increased FDG sensitivity translates into more biopsy referrals, but since the number of benign tumors greatly exceeds that of malignancies, this type of study would still avoid unnecessary patient morbidity and cost. Therefore, a potential cost effective algorithm for the diagnosis of SPN would be CXR, CT, FDG, and, finally, TTNA.

*Indication 2: Lymph Node Staging.* The operability of patients is based on ipsilateral versus contralateral or mediastinal involvement. Contralateral/mediastinal lymph node involvement or the presence of cervical metastases constitutes a contraindication to surgery, since no survival benefit has been demonstrated in these patients. Also, lymph node status is a significant prognostic parameter for predicting survival expectations.

**Table 6**
**Staging Mediastinal and Hilar Lymph Nodes in NSCLC Patients Using FDG PET**

| Study | | | CT | | PET | |
|---|---|---|---|---|---|---|
| **Author** | **Year** | **No. Patients** | **Sensitivity** | **Specificity** | **Sensitivity** | **Specificity** |
| **Chin** | **1995** | **30** | **56** | **86** | **78** | **81** |
| **Valk** | **1995** | **76** | **63** | **73** | **83** | **94** |
| **Sasaki** | **1996** | **29** | **65** | **87** | **76** | **98** |
| **Bury** | **1996** | **50** | **72** | **81** | **90** | **86** |
| **Guhlman** | **1997** | **46** | **50** | **75** | **80** | **100** |
| **Steinert** | **1997** | **47** | **57** | **94** | **89** | **99** |
| **Vansteenki** | **1998** | **68** | **75** | **63** | **93** | **95** |
| **Wahl** | **1994** | **23** | **64** | **44** | **82** | **81** |
| **Pieterman** | **2000** | **102** | **75** | **66** | **91** | **86** |

CT and MRI have a decreased accuracy for staging bronchogenic cancer since anatomical staging is based on lymph node size, which does not always correlate with tumor involvement. Lesions smaller than 1 cm may be missed, while nodes larger than 2 cm have a 30%-37% chance of being benign inflammatory lesions.[77,78] Therefore size is not necessarily a good indicator of malignancy.

There are numerous studies comparing the accuracy of FDG PET with CT for determining nodal status,[79-84] and a recent meta-analysis established the superior accuracy of metabolic over anatomical staging.[85] (See Table 6.) For example, Pieterman et al. compared PET and CT images in 102 patients with non-resectable NSCLC over a two year period, and concluded that the sensitivity and specificity of PET (91%, 86%) was superior to that obtained for CT (75%, 66%).[86]

*Indication 3: Detection of Distal Metastases.* Since 40% of patients with lung cancer have distant metastases at diagnosis, and, therefore, are not surgical candidates, it is important to correctly identify these patients to avoid inappropriate surgery.

There are problematic areas that have variable FDG uptake, such as the liver, kidneys, bowel, and bladder. However, the pattern of uptake differs from that seen in nodular and metastatic uptake and can be distinguished by the trained physician. In addition, metastases and primary tumors can be demonstrated in a single scan, while CT and MRI require separate imaging procedures.

Marom, et al,[85] found PET to be superior to CT/MRI, with increased accuracy in detecting metastases to bone, lung, adrenal gland, liver, and brain.

In several studies,[81,87] greater than 10% of patients were found to have distant metastases not detected by the conventional battery of diagnostic tests (CXR, CT, MRI, bone scan) and were upstaged to non-surgical status. FDG PET correctly identified 14 of the 19 false positives as benign, resulting in downstaging of these patients for possible curative surgery. Therapy management changes were documented in 41% of patients as a result of PET information.[87]

*Indication 4: Recurrence Diagnosis and Evaluation of Response to Treatment.* The majority of patients with lung cancer have advanced disease at diagnosis, with a 5-year survival rate of 13%. Detection of metachronous lesions and assessment of response to chemotherapy and radiation are paramount for redirecting treatment. Changes in tumor metabolism may be a more reliable indicator of response to treatment than reduction in tumor size.

Treatment-induced radiation pneumonitis results in some increased FDG uptake and may make it difficult to differentiate between persistent tumor and treatment-related inflammation. Although mild diffuse uptake is present, SUV $\geq$2.5 is still adequate to distinguish benign from malignant lesions.

Schiepers[88] compiled data on 520 patients diagnosed with lung cancer between 1997 and 1999. Of 173 patients who had received previous treatment, 138 patients had complete data available for analysis. PET downstaged CT-staged patients in 19% of the cases where CT showed a suspicious mass, whereas a negative PET study suggested radiation changes. The overall accuracy of PET was 74%, compared to 54% for CT, and PET altered the surgical status in 35% of the cases studied.

Hicks[89] evaluated 63 patients in whom recurrence was suspected by either an abnormal CXR[61] or symptomatic changes (2). PET results differed from CT in 68% of the cases, downstaging or upstaging CT-staged patients in 33% and 35% of cases, respectively. Follow-up and pathological data revealed a much higher accuracy for PET (89%) compared to CT (22%). Noteworthy is the finding that a positive FDG PET scan for tumor recurrence was associated with approximately 200% increase in relative death rate.

In January 1998, the Health Care Financing Administration (HCFA) adopted a policy to pay for FDG- PET for the following indications: (1) characterization of indeterminate nodules as benign or malignant, and (2) the initial staging of newly diagnosed NSCLC patients. More recently (December 2000), HCFA issued a National Coverage Decision to allow physicians more autonomy in using PET from diagnosis and staging of lung cancer to assessment of therapy and tumor recurrence.

**Radionuclide Imaging**

$^{67}$Ga Citrate

$^{67}$Ga binds to transferrin and the $^{67}$Ga-transferrin complex then binds to receptors on cell membranes, including tumor cells. Because of phagocytosis by leukocytes, $^{67}$Ga also localizes at sites of infection and inflammation. Although it is taken up by >90% of lung tumors, poor specificity and other limitations, such as slow blood clearance, low contrast image resolution, and dosimetry considerations, limit its utility in diagnosing neoplastic disease.[17]

$^{201}$Tl Chloride

Because of the upregulation of the Na+/K+ pump and ATP requirements in malignant tissue, $^{201}$Tl, a potassium analog, can be used as a metabolic marker. $^{201}$Tl has been used clinically to differentiate between benign and malignant tumors, determine

**Box 2**
**Procedure for $^{99m}$Tc-depreotide Lung Scan***

Patient Preparation
- Hydration
- Spiral CT scan and radiologist review

Radionuclide Injection
- $^{99m}$Tc-depreotide 20mCi (740 MBq) injected intravenously

Flow Imaging
- Posterior
  - 4 second frames, 20 frames
  - 128 x 128 matrix
  - high-resolution collimators
  - dual-head camera
  - Siemens ECAMT
- Anterior/posterior
  - 15 minutes post-injection
  - 15000k images

SPECT study
- 2 – 3 hours post-injection
- per manufacturer's parameters
- dual-head camera
  - 64 stops, 25 seconds per stop

Reconstruction
- Iterative reconstruction

*Courtesy of Our Lady of Lourdes Hospital in Binghamton, NY.

tumor extent, differentiate post-therapeutic fibrosis and recurrence, and assess cell necrosis following therapy.[90-92] $^{201}$Tl mediastinum imaging requires SPECT imaging because of high uptake in the liver and myocardium.[93] Higashi[94] found $^{201}$Tl SPECT sensitivity to be comparable to FDG PET in tumors >2cm, but lower in smaller lesions. $^{201}$Tl is also taken up by inflammatory processes, so specificity is compromised. Dual isotope $^{67}$Ga/$^{201}$Tl has a useful application for tumor detection.[95] They are taken up by both tumors and inflammation, but $^{201}$Tl has a rapid washout in inflammatory lesions, revealing the malignant tumor on delayed imaging.

Because of the low keV energy photons and dosimetry limitations, $^{201}$Tl has an

inferior image quality compared to $^{99m}$Tc-labeled compounds.[96-99]

$^{99m}$Tc-Sestamibi and $^{99m}$Tc-Tetrofosmin

Tumor cells require a tremendous amount of energy to fuel the rapid cell growth and cellular proliferation characteristic of malignancy. $^{99m}$Tc-sestamibi (MIBI) localizes in the mitochondria and accumulates in these metabolically active cells, serving as a tumor marker in carcinomas of the lung and breast, in lymph node metastases, and in gliomas.

Gasparini[100] compared MIBI and CT in the staging of mediastinal lymph node metastases. Sixty-one patients were staged with CXR, CT, fiberoptic bronchoscopy, and SPECT MIBI. Mediastinal lymph node involvement was histopathologically confirmed in 18 of 61 patients. MIBI correctly staged 14 of 18 patients as positive and 42 of 43 patients as negative for lymph node involvement (sensitivity 78%, specificity 97%). CT correctly identified 9 of 18 positive lymph nodes and correctly excluded malignancy in 37 of 43 patients (50% sensitivity, 86% specificity). Therefore, functional imaging using MIBI is more sensitive and specific than anatomic delineation with CT.

A few studies[101] comparing MIBI with both $^{201}$Tl and FDG found them to be equivalent in detecting larger primary lesions of the lung. Although FDG is more expensive than MIBI, and requires a nearby cyclotron and either a dedicated PET scanner or coincidence camera, it is still considered by most clinicians to be a superior diagnostic tool. If FDG is unavailable, then MIBI could be considered as an alternative agent. As a technetium compound, it has superior imaging qualities with better dosimetry considerations than $^{201}$Tl, and comparable cost.

There are some limitations to the use of MIBI as a marker of malignancy. Prior chemotherapy, radiation therapy, corticosteroid use, and the presence of tumor necrosis may result in negative MIBI uptake.[97,98]

MIBI is less reliable than $^{201}$Tl and FDG in detecting malignancy in patients following chemotherapy or radiation, because of the multi-drug resistance factor P-glycoprotein. This limitation has actually provided a new oncological application for MIBI. An inverse relationship was found between the tumor-to-background ratios of MIBI and the density of P-glycoprotein expression in tumor tissues.[102] This P-glycoprotein expression associated with multi-drug resistance (MDR) during chemotherapy may represent the best clinical utility of MIBI in cancer detection.[102,103] MDR and resistance to radiation are major obstacles to the treatment of patients with lung cancer. Using MIBI imaging to identify MDR patients prior to chemotherapy or radiation would be beneficial in excluding therapeutic regimens that would only increase patient morbidity, without effecting positive response.

Tetrofosmin has electrochemical properties similar to MIBI, with increased distribution to mitochondrial rich tissues such as the heart, kidney, liver, skeletal muscle, and many neoplasms. Uptake and retention depend on cellular metabolism, which is enhanced in tumor cells. Recently, a study[104] was designed to determine whether dual isotope SPECT with $^{201}$Tl and $^{99m}$Tc-tetrofosmin ($^{99m}$Tc-TF) could predict radioresistance and MDR in patients with lung cancer. Thirty patients with untreated NSCLC were given $^{201}$Tl (111MBq) and $^{99m}$Tc-TF (370 MBq), scanned at 10 and 120 minutes after simultaneous injection, and then given chemotherapy (cisplatin and etoposide) and radiation. Helical CT and semi-quantitative ROI measured treatment response and tracer retention in the tumor, respectively. $^{201}$Tl retention within the lung cancer was significantly prolonged, while there was more rapid washout of $^{99m}$Tc-TF. Prediction of response to chemoradiotherapy by $^{99m}$Tc-TF was more accurate than that analyzed by $^{201}$Tl. Tumors characterized by high $^{99m}$Tc-TF retention ($\geq$15%) and low $^{201}$Tl retention (<70%) showed a favorable response to

chemoradiotherapy, whereas cancers with low $^{99m}$Tc-TF retention (<-15%) did not respond to therapy. Consequently, MIBI and $^{99m}$Tc-TF may be valuable tools to identify MDR patients prior to potentially ineffective treatment.

$^{99m}$Tc-Depreotide

Somatostatin, produced by the hypothalamus and pancreas, binds to specific receptors to inhibit secretion of hormones and growth factors. The receptors are found in the CNS, pituitary, pancreas, and mucosa of the GI tract.[105] Most neuroendocrine tumors (including SCLC)[106] and their metastases exhibit increased expression of these somatostatin type receptors (SSTRs) with avid *in vitro* binding of somatostatin. Because of rapid *in vivo* degradation, the synthetic somatostatin analog octreotide was developed, which was more resistant to degradation. Neuroendocrine tumor localization using {$^{111}$In-DTPA-D-Phe-1}-octreotide (Octreoscan®; Mallinckrodt, St. Louis, MO) has been well documented[106-110] with more avid binding of neoplasms than granulomatous tissues.[111-114] The disadvantages of using $^{111}$In (relatively long half-life of 2.8 days, lower resolution, higher cost, and less than optimal imaging properties) have prompted the search for a $^{99m}$Tc-somatostatin analog.

$^{99m}$Tc-depreotide is a small synthetic peptide (1,358 d) with a somatostatin-binding domain for SSTR subtypes 2,3,and 5, which forms a stable ligand with Tc.[115] $^{99m}$Tc-depreotide has a Tp of 6 hours and rapid blood clearance (4.3% remaining at 1 hour post-injection), with a small amount of renal excretion (6.5% at 24 hours),[116] optimal dosing properties, high contrast SPECT resolution, and the benefit of early imaging. $^{99m}$Tc-depreotide has a higher affinity for somatostatin receptors and NSCLC lesions

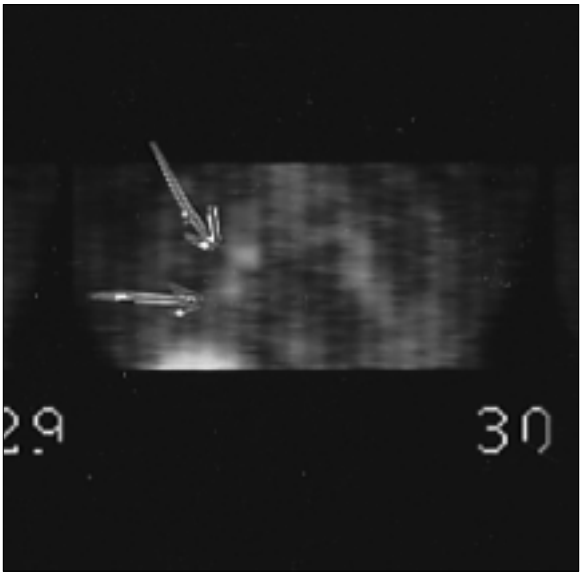


***Figure 2.A.*** Seventy-one-year old female with history of chest pain and shortness of breath for 3 weeks. CT shows a 2-cm nodule of the left lung base and two small 5-10 mm nodules, one at the upper lobe and one in the right lower lobe. There is some mild right hilar adenopathy and a small enlarged lymph node. All are of indeterminant etiology.

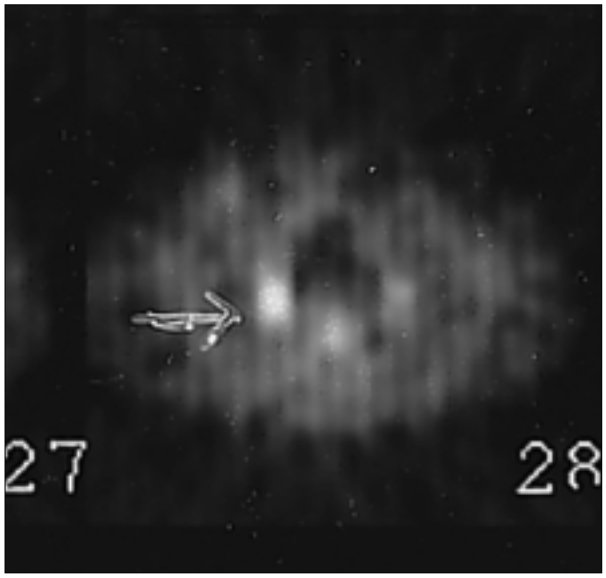


***Figure 2. B.*** $^{99m}$Tc-Depreotide study shows an area of increased uptake, which correlates, with the position of the 2 cm nodule noted on CT. Also, there is some increased activity at the right hilum. Recommendation is for percutaneous biopsy. Reprinted courtesy of St. Joseph's Hospital, Elmira, NY.

than $^{111}$In-pentetreotide.[117]

As SSTR distribution is ubiquitous throughout normal tissues in the respiratory tract,[118] it is recommended that CT be used as a marker of suspicious lesions to guide $^{99m}$Tc-depreotide functional imaging studies. $^{99m}$Tc-depreotide uptake in a nodule seen on CT will also give a stronger indication for biopsy.

Blum, et al,[119] compared the non-invasive characterization of SPNs in 30 high risk patients, using $^{99m}$Tc-depreotide and the "Gold Standard" of tissue histology. While previous studies were criticized for not including patients with proven benign disease to adequately determine specificity, this study included 18 such patients. With a sensitivity of 93% and specificity of 88%, nodules <2cm were consistently correctly identified as malignant, and only 2 false positive studies were obtained (patients with tuberculosis and coccidioidomycosis). Pneumothoraces caused by CT-guided biopsy occurred in 4 patients with lesions found to be benign and correctly characterized by $^{99m}$Tc-depreotide. Given the high sensitivity demonstrated, a negative $^{99m}$Tc-depreotide study would obviate the need for invasive tissue sampling. FDA approval was then granted for the use of $^{99m}$Tc-depreotide for the characterization of SPNs.

In a larger study,[120] Blum evaluated 114 patients with SPNs ≤6cm, using $^{99m}$Tc-depreotide SPECT and histologic tissue examination. $^{99m}$Tc-depreotide correctly characterized 85 of 88 patients with histologically proven malignant neoplasms (96.6% sensitivity), with 3 false negative studies, due to adenocarcinoma. $^{99m}$Tc-depreotide correctly excluded malignancies in 19 of 26 patients with benign lesions (specificity 73.1%), with 7 false positives (6 granulomas, 1 hamartoma). SSTRs have been identified in epithelioid cells of infection and noninfectious granulomatous processes,[121] therefore, subclinical, but active granulomas can give false positive results. Both the sensitivity and specificity compare favorably to FDG PET data. $^{99m}$Tc-depreotide correctly identified malignant lesions in the range of 0.8cm to 6cm, the false negative adenocarcinomas were ≤2cm. $^{99m}$Tc-depreotide also correctly characterized the single case of bronchoalveolar carcinoma missed by FDG PET. This could be due either to the low metabolic activity of this tumor type or to the independence of SSTR expression from metabolic activity.[120] The false positives in patients with active inflammatory granulomatous disease may be due to increased metabolic activity (PET), and either somatostatin overexpression or increased binding in activated leukocytes ($^{99m}$Tc-depreotide).

Handmaker, et al,[122] compared the ability of $^{99m}$Tc-depreotide vs. FDG PET to differentiate between malignant or granulomatous SPNs. Eight patients with SPN >1cm underwent CT, $^{99m}$Tc-depreotide and PET scan, and biopsy. In 2 malignant patients, uptake was seen in both $^{99m}$Tc-depreotide and FDG, whereas true negative $^{99m}$Tc-depreotide and PET scans were obtained in 3 patients with granulomatous disease. In the 3 patients with granulomas, false positive uptake was observed in both scans, but 2 of the 3 patients had metabolically active disease (SUV 4.7 and 3.5).

Gambhir[123] developed a cost/benefit model that demonstrated significant cost savings using FDG PET, and recently suggested that $^{99m}$Tc-depreotide SPECT was more accurate and cost effective than FDG PET in the evaluation of SPNs within the range of probability of 20% to 70%. In the <20% probability group, CXR is the most cost effective, while in the >70% group thoracotomy should be used.

To date, most of the studies using $^{99m}$Tc-depreotide have revolved around the characterization of SPNs, and there are few clinical studies available on the use of $^{99m}$Tc-depreotide in the staging of lymph node involvement, tumor recurrence, or the

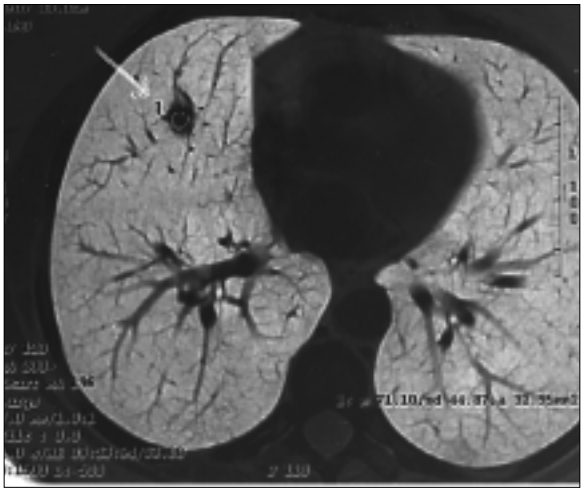

***Figure 3. A.*** The patient is a 61-year-old female who is status-post therapy for SCLC of the lung with good response to radiation and chemotherapy. Spiral CT with contrast was performed. Interstitial changes are noted in the right lung, probably secondary to radiation therapy. There is a 1.6 x 1.2 cm mass in the region of the right middle lobe, not present on the CT performed 10 months previously.

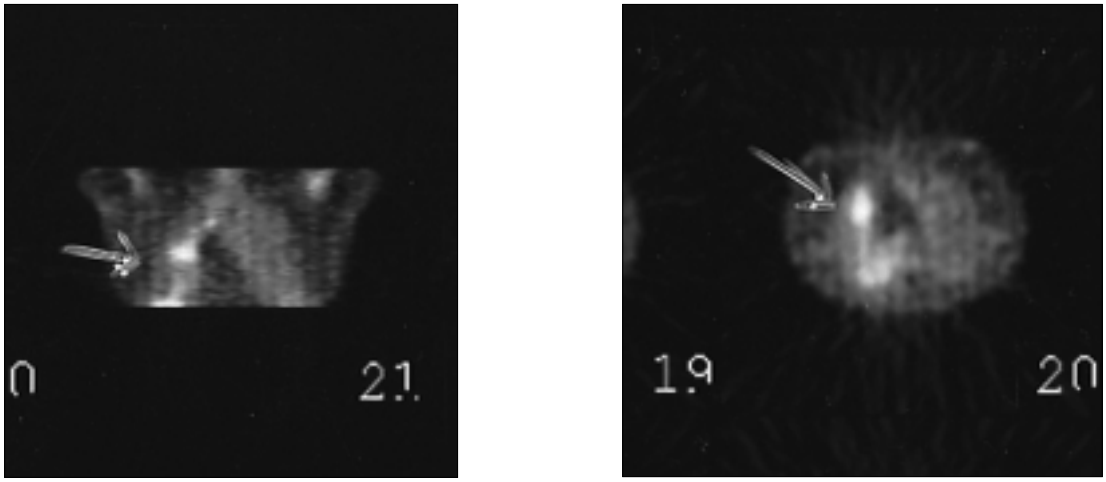


***Figure 3. B.*** $^{99m}$Tc- Depreotide study shows a small mass in the anterior portion of the right lung with significant uptake, indicating recurrence of lung cancer. Reprinted courtesy of St. Joseph's Hospital, Elmira, NY.

evaluation of chemotherapeutic response. Given HCFA endorsement of Medicare coverage for FDG for detecting and staging NSCLC, FDG should be the radiopharmaceutical of choice for these indications. If lack of availability precludes the use of FDG for SPN diagnosis, $^{99m}$Tc-depreotide would be a suitable alternative. Although $^{99m}$Tc-depreotide has all but replaced both MIBI and $^{99m}$Tc-TF for detection of SPNs, identification of MDR remains an important indication for these two radiopharmaceuticals.

## CONCLUSION

The diagnosis and treatment of lung cancer are global health care concerns. With such a poor overall survival rate, it is imperative that measures of early detection be perfected and be widely available. Functional imaging results in greater accuracy over conventional anatomical diagnostic methods for the staging and diagnosis of lung cancer. The ideal algorithm for the diagnosis, staging and treatment of lung cancer would be: CXR, CT, FDG PET or other functional imaging agent, CT-guided biopsy, followed by

appropriate treatment such as surgical extirpation and/or chemotherapy. Using this cost-effective algorithm, functional imaging will decrease the number of biopsies and surgical resections performed on patients with benign pulmonary lesions.

During the search for the ideal functional imaging tool, the following radiopharmaceuticals have been evaluated: $^{67}$Ga, $^{201}$Tl, MIBI, $^{99m}$Tc-TF, FDG, and $^{99m}$Tc-depreotide. Although $^{67}$Ga is sensitive for detecting lung tumors, poor specificity and other limitations, such as slow blood clearance, low contrast image resolution, and dosimetry considerations, limit its utility in diagnosing neoplastic disease. $^{201}$Tl has demonstrated efficacy in the detection of larger SPNs, but because of the low keV energy photons and dosimetry limitations, has an inferior image quality compared to $^{99m}$Tc-labeled compounds. MIBI and $^{99m}$Tc-TF may be valuable tools to identify MDR patients prior to potentially ineffective treatment.

FDG PET indications include the pre-operative diagnosis of single pulmonary nodules, the assessment of mediastinal lymph node involvement, the detection of distant metastases, tumor recurrence, and for evaluating chemotherapeutic response. Although less costly than $^{99m}$Tc-depreotide, FDG is more expensive than MIBI, $^{99m}$Tc-TF, and $^{201}$Tl, and requires both a nearby cyclotron and either a dedicated PET scanner or coincidence camera. However, FDG is still considered by most clinicians to be the "Gold Standard" diagnostic tool, and should be considered as the optimal first-line functional imaging agent. Recently, $^{99m}$Tc-depreotide has demonstrated comparable efficacy in detecting even small pulmonary lesions, and its clinical utility is expected to increase as more indications are researched.

Certainly, the future of radiolabeled peptide compounds looks promising. As the chemistry of labeling peptides becomes increasingly sophisticated, it may be possible to label highly selective compounds with a diagnostic isotope to identify and locate the lesion, followed by a therapeutic isotope for targeted radiotherapy, thereby rendering non-selective chemotherapy obsolete.

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**QUESTIONS**

1. Which of the following agents is not a potential cause of lung cancer?
   a. Asbestos
   b. Aromatic hydrocarbons
   c. Ionizing radiation
   d. Beta-carotene

2. Which of the following statements is true?
   a. SCLC accounts for the majority of lung cancer cases.
   b. SCLC is associated with the best overall prognosis of the 4 primary histologic types.
   c. Most patients with SCLC are candidates for surgery.
   d. None of the above.

3. Which of the following are invasive procedures for tissue sampling?
   a. Thorascopy
   b. TTNA
   c. CT
   d. A and B

4. Which of the following statements concerning lung cancer classification is true?
   a. Squamous cell lesions usually arise in the lung periphery.
   b. Adenocarcinomas and large cell carcinomas are the cell types most likely to metastasize to the brain.
   c. Adenocarcinoma is the most frequently occurring cell type in smokers and males.
   d. Squamous cell lesions are the most likely to metastasize to distant organs.

5. Which of the following statements is true?
   a. Lung cancer is second only to breast cancer as the leading cause of cancer deaths in females.
   b. Smoking cessation campaigns have lowered the incidence of lung cancer by 28% in the last 20 years.
   c. The five-year survival rate for patients diagnosed with lung cancer is 14% for whites, 11% for blacks, and remains largely unchanged over the past 20 years.
   d. Approximately 11 – 14% of patients will have advanced lung cancer at diagnosis.

6. Which of the following is true concerning squamous cell carcinoma?
   a. Hypercalcemia occurs commonly.
   b. Characterized by keratinization and "pearls."
   c. Can metastasize to mediastinal lymph nodes, liver, and adrenal glands.
   d. All of the above.

7. Which of the following represent paraneoplastic syndromes?
   a. Horner's syndrome
   b. Superior vena cava syndrome
   c. Pancoast's syndrome
   d. SIADH

8. What would be the appropriate staging for a NSCLC patient with a CT positive for a primary lesion in the left upper lobe, a nonmalignant pleural effusion, and who is negative for both lymph node involvement and distant metastases?
   a. IIB
   b. IIIA
   c. IIIB
   d. IV

9. Which of the following statements concerning SCLC is false?
   a. SCLC has the most aggressive clinical course of all pulmonary tumors.
   b. Neurosecretory granules and neurofilaments are found in electron microscopy
   c. Chemotherapy results in a 5-year survival rate of 30 – 35%.
   d. Paraneoplasms are common in SCLC.

10. Surgery would be considered appropriate for which of the following staged NSCLC patients?
    a. T2N1M0
    b. T2N3M0
    c. T3N2M1
    d. A and B

11. Tumor cells are metabolically active with increased:
    a. Protein and nucleic acid syntheses
    b. Glucose-6-phosphatase
    c. Hexokinase
    d. A and C

12. Patient preparation for an $^{18}$FDG whole-body PET scan includes:
    a. Fasting for 4 to 12 hours prior to the scan
    b. Diuresis prior to injection
    c. Post-injection hydration
    d. A and B

13. Which of the following is true about TNM staging in patients with NSCLC?
    a. Group IIB includes patients with larger tumors and negative lymph node involvement (T3N0).
    b. Tumor invasion of the mediastinum constitutes group IIIA.
    c. T2N2M1 patients are classified as Stage IV disease
    d. A and C

14. Which of the following statements about $^{18}$FDG uptake and image interpretation are true?
    a. Co-administration of $^{18}$FDG and insulin to a patient with high serum glucose results in increased tumor uptake.
    b. Quantitative measures of absolute glucose values have clinical utility than either qualitative or semi-quantitative methods.
    c. The SUV is an uptake value that is normalized for patient weight and imaging dose.
    d. Chronic hyperglycemia has been demonstrated to inhibit $^{18}$FDG uptake by 50%.

15. The indications for $^{18}$FDG PET in the diagnosis of lung cancer include:
    a. Identification of malignancies in lesions found to be indeterminant from CT.
    b. Staging of the mediastinum, including lymph node involvement
    c. Detection of distant metastases and tumor recurrence.
    d. All of the above.

16. In which of the following cases would you expect a false positive $^{18}$FDG PET study?
    a. Tumors with a low metabolic activity
    b. Active tuberculosis
    c. Acute hyperglycemia
    d. Bronchioalveolar carcinoma

17. Which statements support the notion that functional imaging is superior to anatomical imaging modalities?
    a. Lymph node size does not always correlate with tumor involvement.
    b. Functional changes often precede anatomical changes.
    c. Tumor necrosis may resemble a viable tumor mass on anatomical imaging.
    d. All of the above.

18. What factors could result in negative MIBI uptake?
    a. Prior chemotherapy
    b. Corticosteroid use
    c. Tumor necrosis
    d. All off the above

19. The advantage of using $^{99m}$Tc-depreotide over $^{111}$In-pentetreotide include:
    a. Relatively long half-life of 2.8 days
    b. Higher resolution and the use of early imaging
    c. The superior tumor-to-background ratio of the delayed images
    d. All of the above

20. Which factor limits the use of $Ga^{67}$ in tumor imaging?
    a. Poor sensitivity
    b. Poor specificity
    c. Binding to leukocytes
    d. B and C

21. Which of the following statements about $Tl^{201}$ in tumor imaging is <u>false</u>?
    a. It is a potassium analog and can be used as a metabolic marker.
    b. SPECT imaging is required, because of high uptake in the liver and myocardium.
    c. It is taken up by tumors and sites of inflammation.
    d. It has a rapid washout in tumor imaging; therefore early imaging is required to detect the tumor.

22. Which of the following is true about multidrug resistance (MDR)?
    a. Retention of $^{99m}$Tc-MIBI/Tf in delayed imaging predicts a favorable response to chemotherapy.
    b. Rapid washout of $^{99m}$Tc-MIBI/Tf predicts a favorable response to chemotherapy.
    c. Retention of $Tl^{201}$ in delayed imaging indicates MDR.
    d. Washout of $Tl^{201}$ in delayed imaging indicates MDR.

23. Which of the following is true about $^{99m}$Tc-depreotide?
    a. Delayed imaging is required for an adequate tumor-to-background ratio.
    b. Active granulomatous disease may yield false positive results.
    c. Small tumors may give false positive results.
    d. Tumors with low metabolic activity may give false positive results.

24. Which of the following diagnostic algorithms would be most cost effective in terms of patient morbidity and healthcare costs?
    a. CXR => Bronchoscopy => 18FDG PET => CT
    b. Bronchoscopy => CXR => CT => $^{99m}$Tc-depreotide
    c. CXR => CT => $^{18}$FDG PET => CT-guided biopsy
    d. TTNA => CT =>$^{18}$FDG PET => $^{99m}$Tc-depreotide

25. A patient with a 20 pack-year history of smoking presents to the emergency room complaining of shortness of breath, an increase in intensity and frequency of his cough, and blood-streaked sputum. The patient has been to the hospital previously with CXRs on file. CXR reveals bronchial narrowing, a large mass infiltrating the lung parenchyma near the mediastinum, increased in size since the previous CXR, and gross lymph node enlargement. The most reasonable patient management would be:
    a. Give him Robitussin-DM® or albuterol inhaler and send him home, since he probably just has a cold and chest congestion.
    b. Obtain spiral CT scan and a battery of laboratory tests (CBC, U/A, LFTs, serum calcium, alk phos). Schedule $^{99m}$Tc-depreotide scan and consider a follow-up bone scan and ultrasound of the abdomen, MRI of brain.
    c. Treat patient symptomatically, then schedule an immediate mediastinotomy and biopsy, with follow-up bone scan to detect presence of metastases.
    d. Perform rigid bronchoscopy, CBC, U/A, and bone scan

26. Which of the following are potential sites of metastases from primary bronchogenic cancer?
    a. Liver
    b. Adrenal glands
    c. Bone
    d. A and c only.

27. A patient's performance status is re-evaluated six months post a partial lung resection. The ECOG grade changes from 2 to 3, while the Karnofsky rating changes from 60 to 50. This most likely represents _____ in patient performance status.
    a. A decline
    b. An improvement

28. Which of the following conditions could produce a false negative [18F]FDG study?
    a. Bronchioalveolar cell carcinoma
    b. Sarcoidosis
    c. Wegener's granulomatosis
    d. None of the above

29. What is the rationale for using functional imaging to detect bronchial neoplasms?
    a. Physiologic and biochemical changes occur before anatomical changes.
    b. Earlier detection of disease at the potentially curable stage of the SPN.
    c. Decreased morbidity associated with invasive procedures.
    d. All of the above.

30. Your hospital has just acquired a coincidence camera. Your radiopharmaceutical options for imaging neoplastic nodules in the lung parenchyma include:
    a. [18F]FDG PET
    b. 99mTc-depreotide
    c. MDP
    d. Two of the above

31. Which of the following are extrapulmonary signs and symptoms associated with metastatic involvement of lung cancer?
    a. Hemoptysis
    b. Spinal cord compression
    c. Horner's syndrome
    d. Pancoast's syndrome

32. Despite more stringent regulation of cigarette advertisements, the incidence of smoking related lung cancer has not significantly decreased.
    a. True
    b. False

33. Which histologic lung cancer type is associated with the worst prognosis?
    a. Squamous cell
    b. Adenocarcinoma
    c. Large cell
    d. Small cell

34. False positive [18F]FDG PET /99mTc-depreotide studies in patients with active granulomatous disease may be due to:
    a. Somatostatin overexpression
    b. Increased binding to activated leukocytes
    c. Increased metabolic activityd.
    d. All of the above

35. Which of the following statements about 99mTc-depreotide and somatostatin receptor expression is False?
    a. 99mTc-depreotide binds to SSTR subtypes 2,3, and 5
    b. 99mTc-depreotide has a higher affinity for somatostatin receptors than does 111In-pentetreotide.
    c. Because of the limited number of somatostatin receptors in the lung, 99mTc-depreotide will only bind to lung neoplasms and active inflammatory lesions.
    d. None of the above.

36. Chest x- rays have proven to be an effective screening tool for the early diagnosis of lung cancer.
    a. True
    b. False

37. Which of the following represents an inappropriate radiopharmaceutical dose?
    a. 16 mCi of [18F]FDG for a dedicated PET camera
    b. 7 mCi of [18F]FDG for a coincidence camera
    c. 7 mCi of 99mTc-depreotide
    d. All of the above

38. Important prognostic indicators of disease progression include:
    a. Stage of disease
    b. Post-treatment performance status
    c. Weight loss
    d. All of the above.

39. How does dual isotope 67Ga/201Tl aid in lung tumor detection?
    a. They are taken up by both tumors and inflammatory lesions, but 67Ga has a rapid washout in inflammatory lesions, revealing the malignant tumor on delayed imaging.
    b. They are taken up by both tumors and inflammatory lesions, but 201Tl has a rapid washout in inflammatory lesions, revealing the malignant tumor on delayed imaging.
    c. They are taken up by both tumors and inflammatory lesions, but 67Ga has more intense tumor accumulation, revealing the malignant tumor on early imaging.
    d. They are taken up by both tumors and inflammatory lesions, but 201Tl has more intense tumor accumulation, revealing the malignant tumor on early imaging.

40. Which of the following statements concerning MIBI and TF is False?
    a. Both accumulate in metabolically active cells
    b. Both can be markers for neoplasms
    c. Only MIBI has demonstrated clinical utility in detecting MDR
    d. None of the above