A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer

Gonzalo V. Gonzalez-Stawinski, MD^a

Anthony Lemaire, MD^a

Faisal Merchant, BS^a

Elizabeth O'Halloran, BS^a

R. Edward Coleman, MD^b

David H. Harpole, MD^a

Thomas A. D'Amico, MD^b

See related editorial on page 1700.

From the Division of Cardiothoracic Surgery, Department of Surgery,^a and the Division of Nuclear Medicine,^b Duke University Medical Center, Durham, NC.

Read at the Eighty-second Annual Meeting of The American Association for Thoracic Surgery, Washington, DC, May 5-8, 2002.

Received for publication June 3, 2002; revisions requested July 15, 2002; revisions received Sept 9, 2002; accepted for publication Sept 17, 2002.

Address for reprints: Thomas A. D'Amico, MD, Duke University Medical Center, Box 3496, Durham, NC 27710 (E-mail: damic001@mc.duke.edu).

J Thorac Cardiovasc Surg 2003;126:1900-5

Copyright © 2003 by The American Association for Thoracic Surgery

0022-5223/2003 \$30.00 + 0

doi:10.1016/S0022-5223(03)01036-5

Objectives: Positron emission tomography has been demonstrated to improve the detection of distant metastases in patients with lung cancer. This study compares the efficacy of PET to mediastinoscopy in mediastinal staging of patients with non-small cell lung cancer.

Methods: Between May 1995 and May 2000, positron emission tomography was performed on 1988 patients with known or suspected non-small cell lung cancer at Duke University Medical Center. Cervical mediastinoscopy was subsequently performed in patients without demonstrable evidence of distant metastases. The efficacy of mediastinal staging was analyzed by comparing the prospective results of positron emission tomography with the histopathologic results of mediastinoscopy by nodal station.

Results: In this study 202 patients with non-small cell lung cancer (116 of whom were male) underwent mediastinoscopy after positron emission tomography. Of the 65 patients with positive results of positron emission tomography, only 29 patients had positive results of mediastinoscopy in the corresponding nodal station. Of the 137 patients with negative results of positron emission tomography, 16 patients were demonstrated to have N2 or N3 disease. The sensitivity, specificity, positive and negative predictive values, and accuracy for positron emission tomography were 64.4%, 77.1%, 44.6%, 88.3%, and 74.3%, respectively. Histologic findings in patients with non-small cell lung cancer and false-positive results of mediastinal positron emission tomography included granulomatous inflammation, sinus histiocytosis, and silicosis.

Conclusions: Positron emission tomography neither confirms nor excludes involvement of the mediastinum in patients with non-small cell lung cancer. Cervical mediastinoscopy with lymph node biopsy remains the criterion standard for mediastinal staging.

The treatment of lung cancer, the most common cause of death by malignancy in both men and women in the United States,¹ is determined by the stage of disease. In the current TNM staging system for non-small cell lung cancer (NSCLC), which considers the size and location of the primary tumor, the involvement of regional lymph nodes, and the presence of distant metastases, pathologic staging is considered more accurate than clinical or radiographic staging.² Although radio-

graphic staging frequently underestimates the extent of disease, positron emission tomography (PET) may offer advantages in the staging of lung cancer.³

The applications of PET in the staging of NSCLC include evaluation of indeterminate pulmonary nodules,³⁻⁶ mediastinal staging,⁷⁻¹⁰ assessment of distant metastases,^{11,12} and restaging for treatment response and recurrence.¹³⁻¹⁵ The utility of PET in staging the mediastinum is controversial. Mediastinoscopy has been considered to be the standard for staging of the mediastinum,^{16,17} but it has been suggested that PET may replace mediastinoscopy in some cases.¹⁰ This study is a comparative analysis of PET and mediastinoscopy in staging NSCLC.

Patients and Methods

Patient Selection

The records of all patients who underwent PET at Duke University Medical Center for the evaluation of known or suspected lung cancer were reviewed. Those patients who subsequently underwent cervical mediastinoscopy, extended cervical mediastinoscopy, or anterior mediastinotomy were selected for analysis. The PET scans were then compared with the pathologic results obtained at mediastinoscopy to determine the sensitivity, specificity, positive and negative predictive values, and accuracy. This study was approved by Duke University Medical Center Institutional Review Board.

PET Imaging

All PET studies were performed after fasting for at least 4 hours. PET was performed on an Advance tomographic scanner (GE Medical Systems, Milwaukee, Wis). Transmission scans were obtained over the chest and upper abdomen with rotating germanium 68 pin sources, either before or after isotope administration. Emission images of the chest and upper abdomen were obtained 30 to 60 minutes after the intravenous administration of 10 to 12 mCi of fluorodeoxyglucose F 18 (FDG).

Two-dimensional, non-attenuation-corrected and measured attenuation-corrected images were obtained from the skull base through the proximal thighs. Imaging was performed with reconstruction in the sagittal, axial, and coronal planes. The thoracic images were divided into three regions: lung, hilum, and mediastinum. Serum glucose concentrations were analyzed in all patients before FDG administration, and only patients with glucose concentrations in the normal range underwent PET scan. FDG uptake was considered to be positive in the mediastinum if tracer activity was significantly higher than mediastinal background activity (Figure 1). All studies were interpreted by a nuclear radiologist who was blinded to the histologic results. Results of the PET scans were compared by nodal station with histopathologic results after mediastinoscopy.

Mediastinoscopy

Cervical mediastinoscopy, extended cervical mediastinoscopy, and anterior mediastinotomy were performed on patients for pathologic staging of known or suspected lung cancer, and results were recorded according to the revised International Staging System.^{2,18} The indications for mediastinoscopy in this population included

Figure 1. Positive PET scan result. FDG uptake was considered to be positive in mediastinum if tracer activity was significantly higher than mediastinal background activity.

the presence enlarged lymph nodes (short axis >1 cm) on computed tomographic (CT) scan, T2 or T3 tumors, medically high-risk patients, patients to be enrolled on induction therapy protocols, and hilar or mediastinal involvement on PET scan. The only anatomic contraindication was the presence of a permanent tracheostomy. Patients found to have metastatic disease on PET were excluded.

Statistical Analysis

The diagnostic efficacy of PET scanning relative to mediastinal lymph node biopsy was calculated with sensitivity, specificity, positive and negative predictive values, and accuracy.

Results

Between May 1995 and May 2000, a total of 1988 patients underwent FDG-PET scans at Duke University Medical Center for the staging of known or suspected lung cancer. Of those 1756 patients were excluded from our study: 1053 patients had further workup outside our institution, 667 patients were found to have stage IV disease, 30 patients underwent mediastinoscopy before PET, and 5 patients had a tracheotomy that precluded mediastinoscopy.

Thus 202 patients underwent mediastinoscopy with lymph node biopsy (mean 4.5 stations/patient). There were 116 male and 86 female patients, with a mean age of 64 years (range 31-90 years). The mean interval between PET and mediastinoscopy was 15.4 days. No patients were unavailable for follow-up. Median duration of follow-up was 12.5 months (mean 15 months; range 2-86 months). Before the operation, there were 147 patients with known lung cancer, 51 patients with indeterminate lung nodules, and 5 patients with a lung mass and history of extrapulmonary malignancy in whom the diagnosis of primary lung cancer was suspected. After the operation, there were 151 patients with the diagnosis of lung cancer (Table 1). Histologic subtypes included adenocarcinoma (n = 69), squamous cell carcinoma (n = 45), non-small cell carcinoma (n = 15), large cell carcinoma (n = 8), small cell lung cancer (n = 6)

TABLE 1. Final pathologic diagnoses of patients who underwent mediastinoscopy

Malignant diagnoses	160
Adenocarcinoma	69
Squamous cell carcinoma	45
NSCLC*	15
Large cell carcinoma	8
Small cell lung cancer	6
Adenosquamous carcinoma	4
Atypical carcinoid	3
Metastatic melanoma	3
Metastatic colon carcinoma	2
Lymphoma	2
Bronchoalveolar carcinoma	1
Malignant nerve sheath tumor	1
Metastatic breast cancer	1
Benign diagnoses	42
No malignancy*	14
Obstruction or pneumonia	6
Granulomatous disease	5
Centrilobular emphysema	4
Inflammatory infiltrate	3
Histoplasmosis	2
Aspergillosis	2
Histiocytosis	2
Pulmonary hamartoma	1
Mycobacteria	1
Pneumoconiosis	1
Silicosis	1
Total	202

*Not otherwise specified.

TABLE 2. Results of mediastinal PET scan and mediastinoscopy

	PET positive	PET negative	Total
Mediastinoscopy positive	29	16	45
Mediastinoscopy negative	36	121	157
Total	65	137	202

adenosquamous carcinoma (n = 4), atypical carcinoid (n = 3), and bronchoalveolar carcinoma (n = 1).

The results of PET and mediastinoscopy are detailed in Table 2. Among the 202 patients studied, 65 patients (32.2%) were judged to have a mediastinum that was positive by PET scan. However, only 29/65 patients (44.6%) had positive biopsy results at mediastinoscopy. The 36 patients with positive mediastinal PET and negative mediastinoscopy results (false-positive rate 55.4%) were analyzed. Thirty-five patients (97.2%) underwent surgical exploration and mediastinal lymph node dissection; 2 of them (5.7%) were found to have mediastinal lymph node metastases not detected by mediastinoscopy. One patient was found to have a single positive level 8 lymph node, although this was not the station that was positive on PET; the second patient had micrometastatic disease at level 7, missed at

TABLE 3. Sensitivity, specificity, positive and negative predictive values, and accuracy of PET scan

Sensitivity	64.4%
Specificity	77.1%
Positive predictive value	44.6%
Negative predictive value	88.3%
Accuracy	74.3%

frozen-section analysis. Of the remaining 33 patients, 20 have no evidence of disease at a median follow-up of 12.5 months. Nine patients had distant metastases develop without evidence of regional nodal recurrence, and 1 patient died with no evidence of disease in the postoperative period. Finally, 4 patients had granulomatous disease. Benign processes that may have contributed to the false-positive PET scan results in patients with cancer include obstruction or pneumonia (n = 6), granulomatous disease (n = 5), and silicosis (n = 1). The remainder of the patients with false-positive biopsy results manifested no specific pathologic process within the mediastinal lymph nodes.

Of the 137 patients that had a negative mediastinum by PET, 16 had positive results on mediastinoscopy (false-negative rate 11.7%). The patients with false-negative PET scan results included the following staging groups: T1 N2 (n = 3), T2 N2 (n = 5), T2 N3 (n = 5), small cell lung cancer (n = 2), and metastatic breast cancer (n = 1). The sensitivity, specificity, positive and negative predictive values, and accuracy of PET scan were 64.4%, 77.1%, 44.6%, 88.3%, and 74.3%, respectively (Table 3).

Discussion

There are four accepted indications for the use of PET in the diagnosis and staging of patients with NSCLC. PET has been used extensively in the evaluation of indeterminate solitary pulmonary nodules.³⁻⁶ In one prospective study, PET had overall sensitivity and specificity to characterize malignant pulmonary nodules of 92% and 90%, respectively.⁶ A recent meta-analysis of seven published series demonstrated sensitivity and specificity of 95% and 81%.³ Furthermore, the degree of FDG uptake, as measured by standardized uptake ratio, has been found to provide important prognostic information independent of clinical stage and size of lesion.⁷

PET has also been applied to detect residual or recurrent disease, predominately after treatment with chemotherapy and radiation. In one study, 113 patients with lung cancer had the disease restaged with PET after the completion of initial therapy.¹⁵ There was a significant difference in survival between those patients with positive scan results after therapy and those with negative scan results. In the future, it may be possible to assess a patient during treatment with chemotherapy and radiation therapy to estimate treatment

response, allowing an earlier opportunity to use an alternate therapy if necessary.

The most effective use of PET to date appears to be in the detection of distant metastases. In one recent series of 105 patients, PET detected unsuspected distant metastases in 26% of patients and changed or influenced the management in 67% of patients with NSCLC.¹¹ In a second series of 102 patients, PET identified distant metastases not found by other methods in 11% of patients and led to upstaging in 42% of cases and downstaging in 20% of cases.¹² The ability of PET to detect metastatic disease is unparalleled; the challenge for this application is to define the appropriate population of potentially operable cases in which to obtain PET for cost-effectiveness.¹⁹

The success of PET in distant metastatic staging has led to the increased use of PET to stage the mediastinum. PET is clearly superior to CT scanning alone in assessing the mediastinum for malignant disease,^{20,21} and various algorithms have been suggested that could reduce the use of mediastinoscopy. Anecdotal reports suggest that patients with positive mediastinal PET scan results may be treated as stage III (with definitive chemotherapy and radiation therapy or with induction therapy followed by surgery), without histologic confirmation of N2 disease or exclusion of N3 disease. There is no evidence in the literature to support this approach.

In a recent study, it was proposed that patients with negative CT and mediastinal PET scan results do not require mediastinoscopy before exploration for resection and mediastinal lymph node dissection.¹⁰ By this reasonable strategy, the authors concluded that the need for mediastinoscopy would be reduced by 12%. Although this study was carefully analyzed, it is not clear what clinical criteria were applied to perform mediastinoscopy, such as T status. The false-negative rate of PET in this study was not fully addressed. It should also be remembered that if the primary tumor does not have significant FDG uptake, the mediastinal lymph nodes should not be expected to uptake FDG, even if involved.

Our study was undertaken to address two issues. Increasingly, patients are being referred to our institution after treatment decisions have already been made on the basis of the results of a mediastinal PET scan, without histologic confirmation. The first objective was to analyze the group of positive PET scan results to determine the false-positive rate, identifying cases inappropriately staged as IIIa or IIIb. The second objective was to analyze the group of negative PET scan results to determine the false-negative rate, identifying patients with undetected N2 or N3 disease who would be inappropriately treated with surgery primarily.

In this study, 202 patients underwent PET staging (for known or suspected lung cancer) and subsequent mediastinoscopy, constituting the study population. Many of the

patients who underwent PET staging were excluded, either because metastatic disease was discovered or because the patients were treated surgically without mediastinoscopy (usually at another institution). The ideal study design would have prospectively registered patients to receive a PET scan followed by mediastinoscopy; because some patients went directly to surgery, selection bias may have limited the denominator in this study, without affecting the numerators: the number of patients with either false-positive or false-negative PET scan results.

Among the 202 patients who underwent PET and subsequent mediastinoscopy, the initial false-positive rate was 55%: of the 65 patients with positive mediastinal PET scan results, 36 had a negative mediastinoscopy. Because the false-negative PET scan results may represent a failure of mediastinoscopy rather than an inaccurate PET study, it is important to include complete follow-up on all potential false-negative results. One patient died after coronary artery bypass grafting, performed before planned pulmonary resection, and 35 underwent exploration. Of these 35 patients, 2 were found to have N2 disease at thoracotomy; thus, the actual false-positive rate was 34 of 65 (52%), although PET did not accurately identify the positive station in one of the patients. Of the remaining 33 patients, 20 are considered to have no evidence of disease, with a median follow-up of 12.5 months. Nine patients had distant metastases develop without evidence of regional nodal recurrence, and 1 patient with died no evidence of disease in the postoperative period. Benign processes that may have contributed to the false-positive PET scan results in patients with cancer include obstruction or pneumonia ($n = 6$), granulomatous disease ($n = 5$), and silicosis ($n = 1$).

From this analysis, it appears that mediastinoscopy failed in only 2 of 65 patients with positive PET scan results (3%). Factors known to be associated with false-positive PET staging include obstructive pneumonia and inflammatory disease.²² It is noteworthy that 4 patients with false-positive PET scan results did not have cancer, and 12 patients with node-negative cancer had benign processes of the mediastinum. A strategy to equate a positive mediastinal PET scan result with stage III disease would result in inappropriate therapy in most (52%) patients in this group.

The false-negative rate in this study was low (11.7%); however, the group included 5 patients with unsuspected N3 disease and 2 patients with small cell lung cancer (all with negative mediastinal lymph nodes on CT and PET), for whom surgical therapy would be considered contraindicated. Although most patients found to have N2 disease had T2 disease ($n = 5$), there were 3 patients with stage T1 N2 in whom the PET and the CT results were considered negative. A strategy to exclude mediastinoscopy in this group would not be reasonable. Unlike other series, our study did not differentiate scans by standardized uptake

values, because our experience has not found that strategy to be advantageous.²³ It is possible that subgroups among the patients with negative mediastinal PET scans could be identified for whom the risk of mediastinal metastases is low enough to justify avoiding mediastinoscopy. A cost analysis, including the costs and risks of mediastinoscopy, would be required to answer this question.

PET represents an important advance in the staging of lung cancer. The use of PET in staging the mediastinum must take into account the significance of false-positive and false-negative results. A positive PET scan result does not necessarily represent malignant disease, and histologic confirmation is always warranted. In this setting, PET may be useful to direct biopsies, especially if initial biopsy results are unexpectedly negative.¹⁰ A negative PET scan result is relatively powerful (negative predictive value 88.3%). Nevertheless, mediastinoscopy may identify N2 or N3 disease in this group of patients. Mediastinoscopy remains the criterion standard in staging the mediastinum in patients with lung cancer.

References

- Jemal A, Thomas A, Murray T, Thun M. Cancer statistics 2002. *CA Cancer J Clin*. 2002;52:23-45.
- Mountain CF. Revisions in the international system for staging lung cancer. *Chest*. 1997;111:1710-7.
- Lowe VJ, Naunheim KS. Positron emission tomography in lung cancer. *Ann Thorac Surg*. 1998;65:1821-9.
- Duhaylongsod FG, Lowe VJ, Patz EF, Vaughn AL, Coleman RE, Wolfe WG. Detection of primary and recurrent lung cancer by means of F-18 fluorodeoxyglucose positron emission tomography (FDG-PET). *J Thorac Cardiovasc Surg*. 1995;110:130-9.
- Dewan NA, Shehan CJ, Reeb SD, Gobar LS, Scott WJ, Ryschon K. Likelihood of malignancy in a solitary pulmonary nodule: comparison of Bayesian analysis and results of FDG-PET scan. *Chest*. 1997;112:416-22.
- Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirschner P, Valk P, et al. Prospective investigation of positron emission tomography in lung nodules. *J Clin Oncol*. 1998;16:1075-84.
- Ahuja V, Coleman RE, Herndon J, Patz EF Jr. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with nonsmall cell lung carcinoma. *Cancer*. 1998;83:918-24.
- Gupta NC, Tamim WJ, Graeber GM, Bishop HA, Hobbs GR. Mediastinal lymph node sampling following positron emission tomography with fluorodeoxyglucose imaging in lung cancer staging. *Chest*. 2001;120:521-7.
- Gupta NC, Graeber GM, Bishop HA. Comparative efficacy of positron emission tomography with fluorodeoxyglucose in evaluation of small (<1 cm), intermediate (1 to 3 cm), and large (>3 cm) lymph node lesions. *Chest*. 2000;117:773-8.
- Kernstine KH, McLaughlin KA, Menda Y, Rossi NP, Kahn DJ, Bushnell DL, et al. Can FDG-PET reduce the need for mediastinoscopy in potentially resectable nonsmall cell lung cancer? *Ann Thorac Surg*. 2002;73:394-402.
- Kalff V, Hicks RJ, MacManus MP, Binns DS, McKenzie AF, Ware RE, et al. Clinical impact of (18)F fluorodeoxyglucose positron emission tomography in patients with non-small-cell lung cancer: a prospective study. *J Clin Oncol*. 2001;19:111-8.
- Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koeter GH, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *N Engl J Med*. 2000;343:254-61.
- Patz EF Jr, Connolly J, Herndon J. Prognostic value of FDG-PET imaging after treatment for non-small cell lung cancer. *AJR Am J Roentgenol*. 2000;174:769-74.
- Akhurst T, Downey RJ, Ginsberg MS, Gonen M, Bains M, Korst R, et al. An initial experience with FDG-PET in the imaging of residual disease after induction therapy for lung cancer. *Ann Thorac Surg*. 2002;73:259-66.
- Patz EF, Lowe VJ, Hoffman JM, Paine SS, Harris LK, Goodman PC. Persistent or recurrent bronchogenic carcinoma: detection with PET and 2-¹⁸F-2-deoxy-D-glucose. *Radiology*. 1994;191:379-82.
- Hammoud ZT, Anderson RC, Meyers BF, Guthrie TJ, Roper CL, Cooper JD, et al. The current role of mediastinoscopy in the evaluation of thoracic disease. *J Thorac Cardiovasc Surg*. 1999;118:894-9.
- Luke WP, Pearson FG, Todd TR, Patterson GA, Cooper JD. Prospective evaluation of mediastinoscopy for assessment of carcinoma of the lung. *J Thorac Cardiovasc Surg*. 1986;91:53-6.
- Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest*. 1997;111:1718-23.
- Scott WJ, Shepherd J, Gambhir SS. Cost-effectiveness of FDG-PET for staging non-small cell lung cancer: a decision analysis. *Ann Thorac Surg*. 1998;66:1876-83.
- Kernstine KH, Stanford W, Mullan BF, Rossi NP, Thompson BJ, Bushnell DL, et al. PET, CT, and MRI with Combix for mediastinal staging in non-small cell lung carcinoma. *Ann Thorac Surg*. 1999;68:1022-8.
- Scott WJ, Gobar LS, Terry JD, Dewan NA, Sunderland JJ. Mediastinal lymph node staging of non-small-cell lung cancer: a prospective comparison of computed tomography and positron emission tomography. *J Thorac Cardiovasc Surg*. 1996;111:642-8.
- Roberts PF, Follette DM, von Haag D, Park JA, Valk PE, Pounds TR, et al. Factors associated with false-positive staging of lung cancer by positron emission tomography. *Ann Thorac Surg*. 2000;70:1154-60.
- Lowe VJ, Hoffman JM, DeLong DM, Patz EF, Coleman RE. Semi-quantitative and visual analysis of FDG-PET images in pulmonary abnormalities. *J Nucl Med*. 1994;35:1771-6.

Discussion

Dr Douglas E. Wood (Seattle, Wash). I congratulate Gonzalez-Stawinski and colleagues at Duke for an important contribution that refines our knowledge of the role of PET scanning in lung cancer staging. The recent enthusiasm with PET imaging mirrors almost exactly the experience that we had with the introduction of CT scanning in the 1970s. Initial reports suggested that CT had sensitivity and specificity for mediastinal lymph node involvement greater than 90% and that mediastinoscopy was no longer necessary. Paradoxically, as experience and technology improved, the reports of accuracy diminished, and nearly all experienced thoracic surgeons still considered mediastinoscopy was necessary to confirm positive mediastinal lymph nodes. Many of us have felt that the poor sensitivity of CT supports the use of routine mediastinoscopy to better direct patients into multimodality protocols and to avoid the morbidity of nontherapeutic thoracotomies.

The initial experience and data with PET again suggested that mediastinoscopy is no longer necessary for lung cancer staging. Most of the early PET articles reported accuracy greater than 90%, but Gonzalez-Stawinski and colleagues have shown us more mature results with careful pathologic correlation. In our own experience reported last year, PET correctly differentiated N0-1 disease from N2-3 disease in 91% of patients, with both positive and negative predictive values of 90%. Although this is better than found in this series, it led us to the same conclusion, that there are high enough incidences of both false-positive and false-negative