The impact of fluorodeoxyglucose F 18 positron-emission tomography on the surgical staging of non-small cell lung cancer

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Objectives: Staging data on patients with non-small cell lung cancer were prospectively collected to evaluate the accuracy and anatomic information provided by fluorodeoxyglucose F 18 positron-emission tomography and its impact on improving the accuracy of surgical staging.

Methods: A total of 142 patients with potentially resectable non-small cell lung cancer were imaged with positron-emission tomography (neck to pelvis). Positron-emission tomographic scans were read prospectively with thoracic computed tomographic comparison. Patients without distant metastases at positron-emission tomography underwent staging with bronchoscopy and mediastinoscopy, with or without mediastinotomy or thoracoscopy. Patients with metastases, pleural implants, or N2 or N3 disease did not undergo primary resection.

Results: Positron-emission tomography revealed unsuspected distant metastases in 24 of 142 patients (16.9%) and unsuspected pleural implants in 6 others. Nodal stage was surgically established in 118 cases. Positron-emission tomography showed that 5 patients had nodal disease not accessible by mediastinoscopy. In 35 (24.6%) of these 142 cases, positron-emission tomography directed the evaluation away from routine bronchoscopy and mediastinoscopy staging that would have resulted in inappropriate treatment selection. Positron-emission tomography correctly differentiated resectable stages IA through IIIA (N1) from stages IIIA (N2) through IV in 88.7% of cases. In identifying N2 or N3 disease, positron-emission tomography had an accuracy of 90.7%, a sensitivity of 80.9%, a specificity of 96%, and positive and negative predictive values of 91.9% and 90.1%, respectively. Of the 8 cases in which positron-emission tomography missed N2 disease, 7 had the disease discovered by mediastinoscopy and 1 had it discovered at thoracotomy.

Conclusions: The diagnostic accuracy of positron-emission tomography-enhanced clinical staging is high. Positron-emission tomography has previously been used primarily to screen for lymph node spread and distant metastases, but it also provides localizing information that allows directed and more sensitive surgical staging and refinement of patient selection for curative resection. Positron-emission tomography and surgical staging play complementary roles in the journey toward more accurate overall staging.

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Lung cancer remains the leading cause of cancer death in the United States, with more than 170,000 new patients and 158,000 deaths in 1999,¹ 80% with non-small cell histologic type. Stage of non-small cell lung cancer (NSCLC) is the most significant factor determining prognosis, management, and operability. The recently revised TNM staging system for lung cancer shows a 5-year survival ranging from 1% for stage IV disease to 67% for completely resected stage IA cancers.² Met-

ulous staging of NSCLC is critical to prevent clinical over-staging and the consequent denial of therapy with curative intent. Accurate staging is also important to avoid clinical understaging and the consequent morbidity, time, and cost associated with ineffective therapies, particularly unnecessary thoracotomy. In addition, accurate staging is necessary for the selection and enrollment of patients in clinical trials. Therefore every means should be used to establish the correct stage of a newly diagnosed lung cancer before initiating therapy.

Clinical staging of NSCLC routinely includes computed tomography (CT) of the thorax. No additional imaging is currently recommended to detect metastatic disease in the absence of clinical or laboratory evidence of distant disease. CT imaging of the thorax allows localization of the primary tumor with respect to anatomic structures, providing valuable information on the primary tumor (T stage) and its resectability. CT also provides an important assessment of mediastinal lymph nodes (N status), although CT alone has been found to have low sensitivity (64%) and specificity (62%) for identification of malignant N2 and N3 lymph nodes.³

Invasive staging, consisting of mediastinoscopy, mediastinotomy, thoracoscopy, and ultimately thoracotomy, provides the ultimate criterion standard for histologic confirmation of staging. Most institutions reserve staging by mediastinoscopy, thoracoscopy, and thoracotomy for evaluation of specific abnormalities detected during preoperative imaging studies. Mediastinoscopy is routinely recommended to confirm or exclude malignancy in enlarged mediastinal lymph nodes in accordance with National Comprehensive Cancer Network NSCLC guidelines.⁴ The utility of mediastinoscopy in the presence of normal-sized mediastinal lymph nodes is more controversial. Even patients with peripheral T1 tumors and no mediastinal adenopathy according to CT may be found to have positive mediastinal lymph nodes in as many as 21% of cases.⁵ Because N2 disease is a strong marker for probable occult distant metastatic disease, many thoracic surgeons routinely perform mediastinoscopy, which provides the opportunity to consider induction therapy before thoracotomy. Several large series have now documented the safety of mediastinoscopy, with a morbidity of 1% to 2% and mortality of 0.05% to 0.1%.^{6,7} In experienced hands mediastinoscopy is extremely accurate, with an average sensitivity of 84%, a specificity of 100%, and a false-negative rate averaging 9% in 10 large series.⁸⁻¹⁷ Primary surgical resection for the patient with NSCLC is not usually performed in the presence of mediastinal lymph node involvement, malignant pleural implants, or distant metastatic disease.

Clinical staging of NSCLC could benefit from both more sensitive and more specific detection of distant metastases, as well as from improved accuracy in mediastinal staging.

In recent years multiple studies have shown that positron-emission tomography (PET) with fluorodeoxyglucose F 18 (FDG) can fulfill both these goals.¹⁸⁻³² It is now well established that FDG PET will detect the presence of unsuspected extrathoracic metastases in 14% to 16.5% of patients with disease otherwise deemed resectable (clinical stage IIIA or less).¹⁸⁻²⁰ The diagnostic accuracy of FDG PET in staging the mediastinum has also been reported in multiple studies.¹⁸⁻³¹ In a meta-analysis of 14 PET studies and 29 CT studies, Dwamena and associates³² reported that PET was significantly more accurate than CT in demonstrating nodal metastases ($P < .001$). The mean sensitivity and specificity were $79\% \pm 3\%$ and $91\% \pm 2\%$, respectively, for PET and $60\% \pm 2\%$ and $77\% \pm 2\%$, respectively, for CT.

Beyond the identification of unsuspected extrathoracic distant metastases and provision of noninvasive mediastinal staging, FDG PET also plays an important role in the surgical staging of potentially resectable NSCLC disease. Although the role of FDG PET in staging NSCLC is often discussed as being mutually exclusive with that of mediastinoscopy, the two procedures can play complementary roles. The impact of FDG PET on the approach to surgical staging and the interplay between FDG PET and the selection of mediastinoscopy or other staging procedures has not been addressed. We reviewed our prospective experience with FDG PET combined with CT and routine mediastinoscopy and examined the impact of PET findings on directing surgical staging procedures and refining staging before thoracotomy.

Methods

Potential subjects were all patients referred with a diagnosis of NSCLC to the thoracic surgery clinics at the University of Washington Medical Center or the Veterans Affairs Puget Sound Health Care System between February 1998 and May 2001. All patients underwent CT imaging of the thorax, and those with potentially resectable NSCLC were referred for imaging with FDG PET. All patients were imaged with FDG PET except for patients with lesions too small (<1 cm) or of insufficient cellularity (not visible on mediastinal windows of CT). These exclusions were intended to ensure adequate quantitation of FDG uptake in the primary lesion. Patients in whom the histologic type was subsequently found to be different from NSCLC or in whom the histologic type could not be confirmed were excluded. Patients with type I diabetes were also excluded. None of these patients had received induction therapy before PET, surgical staging, or resection (except for local brain metastasis). All patients had to be operative candidates if the tumor was found to be stage I or II, or T3 N1 M0. A total of 142 patients satisfied these enrollment criteria.

Positron-Emission Tomographic Imaging

All PET studies were performed with a dedicated whole-body PET tomograph (PET Advance; General Electric Medical Systems, Milwaukee, Wis). Patients were asked to fast for 12 hours before

tracer administration. Two intravenous catheters were placed in opposite arms, one for tracer administration and the other for blood sampling. An initial blood sample was obtained at the time of intravenous catheter placement to screen for abnormally high plasma glucose levels. Just before tracer administration, patients also received 1 mg of lorazepam intravenously to decrease benign muscular uptake in the neck and upper thorax that could compromise image interpretation. Seven to 11 mCi of FDG were infused intravenously during 2 minutes with a Harvard pump (Harvard Apparatus, Inc, Holliston, Mass). After a 45-minute rest period, patients were placed supine in the scanner with the thorax positioned to fit within two contiguous 15-cm wide tomograph fields of view. Imaging always started with a 15-minute emission scan performed over the thoracic field of view encompassing the primary lung cancer. This allowed quantitative analysis of tracer uptake by means of the standard uptake value in the primary tumor in a standard period (45-60 minutes) after injection, to control for the time dependence of the standard uptake value. The other thoracic field of view and the abdomen were also imaged with 10-minute emission scans. Five-minute emission scans were performed over the neck and pelvis. These scans were followed by 15-minute transmission studies over the three fields of view encompassing the chest and abdomen, performed after all emission studies had been completed.

All studies were collected in 2-dimensional imaging mode with scatter septa in place. Real-time random correction with counts obtained with a delayed coincidence window and deconvolution-based scatter corrections supplied by the manufacturer were applied. The raw PET data were reconstructed with the standard filtered back projection available on the PET Advance system. The following reconstruction parameters were used: 12-mm Hanning filter, 55-cm image diameter, and 128×128 array size. Both emission scans and attenuation-corrected scans were reconstructed for each patient. The transmission scan, which is coregistered with the other two scans, was also reconstructed to provide anatomic localization details that might not be easily appreciated on the two other scans. All FDG PET scans were read prospectively on a dedicated workstation by the same experienced reader (H.V.) and with the benefit of comparison with the corresponding thoracic CT scans. The following 5-point scale was used on the attenuation-corrected images for the evaluation of FDG activity in lymph nodes: 1, not identifiable on the imaging workstation; 2, lower activity than mediastinal blood pool activity; 3, equal to minimally greater than mediastinal blood pool activity; 4, greater than mediastinal blood pool activity; and 5, much greater than mediastinal blood pool activity. Lymph nodes with activity levels 4 and 5 were read as malignant, with others read as benign.

Surgical Staging

The imaging and surgical evaluations of patients enrolled in this study are summarized on Figure 1. Patients with stage IV disease according to FDG PET had metastatic status confirmed by either additional anatomic imaging or percutaneous biopsy. Patients without distant metastases at PET but with PET evidence of pleural implants underwent thoracoscopy for confirmation if findings were not confirmed as pleural nodules on subsequent second review of the thoracic CT scan. Patients without distant metastases at PET but with evidence of mediastinal disease in a location that

would not be accessible by mediastinoscopy underwent surgical staging with thoracoscopy, mediastinotomy, or thoracotomy as indicated. All other patients underwent staging with bronchoscopy and mediastinoscopy. Surgical confirmation of the lymph node status by mediastinoscopy was performed in all patients independent of the size of these nodes on chest CT or the presence or absence of uptake by PET imaging. The results of FDG PET imaging in the mediastinum were available to the surgeon before confirmation of the mediastinal nodal status.

Pathologic Examination

All biopsy and resection specimens were reviewed by the pathology departments of the University of Washington Medical Center and the Veterans Affairs Puget Sound Health Care System. The non-small cell nature of each tumor was confirmed, as was the histologic subtype. The T and N statuses for each tumor were assessed.

FDG PET and surgical staging data of these lung cancers were prospectively collected to evaluate the accuracy and disease localizing information provided by PET in planning surgical staging and to compare PET staging with pathologic staging. The impact of this information on surgical staging was also examined. This study was conducted under University of Washington institutional review board approval.

Results

FDG PET was used to stage the disease of 142 patients with NSCLC. The histologic type and lesion size distributions for the patients of this series are as shown in Tables 1 and 2. Of these, 7 patients with a treated solitary brain metastasis were seen for evaluation of resectability of the primary lung cancer. Additional unsuspected extracranial metastases (M1) were identified by FDG PET in 3 of these 7 cases. Of the remaining 135 patients without initial evidence of metastatic disease to the brain, 21 (15.5%) of 135 were found to have metastatic disease by PET. Overall, PET discovered unsuspected M1 disease in 24 (16.9%) of 142 patients (including patients with a treated brain lesion), and no pulmonary resection was performed in these cases. This unsuspected M1 disease was confirmed by biopsy in 5 cases, by CT in 8 cases, by magnetic resonance imaging in 9 cases, and by bone scan in 2 cases.

Eight cases were clinically staged as T4 lesions by CT scan. PET confirmed each of these T4 lesions. PET also found an additional 7 unsuspected cases of T4 disease, 6 with pleural tumor implants. Fourteen of the 15 cases were confirmed (including the 6 cases of pleural involvement), and 8 additional cases of T4 disease that had not been suspected either clinically or by PET were revealed at pathologic examination. Three were tracheal involvement, 2 were great vessel or myocardium involvement, and 3 were "satellite" lesions close to but separate from the main lesion.

The nodal status was proved surgically in 118 cases. Table 3 details the results of the nodal staging by PET relative to the surgicopathologic N stage. PET correctly

Figure 1. FDG-PET–based clinical and surgical staging and management of NSCLC.

TABLE 1. Histologic distribution for the reported cases

Histologic type	No.
Adenocarcinoma	51
Bronchioloalveolar cell	6
Large cell	10
Squamous cell	38
Other (carcinosarcoma)	2
NSCLC not otherwise specified	35
Total	142

TABLE 2. Primary tumor size distribution for the reported cases

Tumor greatest diameter (cm)	No.
≥1, ≤2	22
>2, ≤3	28
>3, ≤4	39
>4	53
Total	142

staged the absolute N status in 83 of 118 cases (70.3%). However, FDG PET correctly differentiated N0 or N1 disease from N2 or N3 disease in 101 (85.6%) of 118 cases (Table 3). Most important, FDG PET correctly differentiated cases with mediastinal lymph node involvement (N2-N3) from those without such involvement (N0-N1) in 107 (90.7%) of 118 cases (Table 3). The data in Table 3 show

that for the identification of mediastinal nodal disease, FDG PET had a sensitivity of 80.9%, a specificity of 96.0%, a positive predictive value of 91.9%, and a negative predictive value of 90.1%. PET correctly differentiated resectable stage IA through IIIA (N1) disease from nonresectable stage IIIA (N2) through IV disease in 126 (88.7%) of 142 cases. PET correctly identified most N0 disease (n = 49/55) but was less accurate for N1 disease (n = 6/21; Table 3).

TABLE 3. Lymph node status at FDG-PET versus pathologic examination

By PET	At pathologic examination				Total
	N0	N1	N2	N3	
N0	49	14	5	0	68
N1	4	6	3	0	13
N2	2	1	22	4	29
N3	0	0	2	6	8
Total	55	21	32	10	118

By PET	At pathologic examination			Total
	N0-1	N2	N3	
N0-1	73	8	0	81
N2	3	22	4	29
N3	0	2	6	8
Total	76	32	10	118

By PET	At pathologic examination		Total
	N0-1	N2-3	
N0-1	73	8	81
N2-3	3	34	37
Total	76	42	118

Of the 118 patients in whom the nodal status was surgically confirmed, 112 underwent a mediastinoscopy. No cases of N3 disease were underestimated as N0 or N1 by PET (Table 3). However, PET underestimated the presence of N2 nodal disease in 8 (6.8%) of 118 patients. In these 8 cases, PET showed no abnormal uptake in the mediastinum and therefore provided no localizing information to guide surgical staging. Mediastinoscopy identified 7 (87.5%) of the 8 positive N2 lymph nodes that were negative by PET criteria, and in 1 (12.5%) of the 8 a positive subcarinal lymph node was missed at mediastinoscopy and discovered at thoracotomy.

In 5 cases PET identified mediastinal lymph node involvement at unique locations that were neither accessible to nor identified by the standard surgical staging with bronchoscopy and mediastinoscopy (2 posterior subcarinal lymph nodes, 2 aortopulmonary window nodes, and 1 paraesophageal node). In these cases the involved node was found either at thoracotomy or thoracoscopy, and no other mediastinal lymph nodes were involved. If one considers these 5 cases together with the 6 cases of unsuspected pleural disease, there were 11 (9.3%) of 118 cases without unsuspected distant metastases for which the standard approach of bronchoscopy and mediastinoscopy would have led to an inaccurate stage.

Discussion

Accurate staging is paramount in assigning the most effective, most efficient, and least morbid therapy for patients with NSCLC. PET correctly differentiated resectable stages IA through IIIA (N1) from nonresectable stages IIIA (N2)

through IV in 126 (88.7%) of 142 cases. FDG PET did not reliably identify N1 disease, with only 6 of 21 cases identified. This lack of sensitivity for N1 disease probably stems from the fact that N1 lymph nodes are usually located close to the primary tumor, and thus their modest FDG accumulation relative to the more intense uptake of the primary mass may be difficult to discriminate. In addition, this low sensitivity for N1 disease may in part result from the small size of intralobar N1 nodes, which are rarely identified on chest CT. Nonetheless, FDG PET accurately differentiated N0 or N1 disease from N2 or N3 disease in 90.7% of cases, and this is the most important differentiation to be made for preoperative treatment planning. Patients with N0 or N1 status are preferentially treated by primary resection without induction therapy, although induction therapy trials for these patients are underway. In the era predating the availability of FDG PET, the N1 status of a tumor was in most instances only discovered on pathologic review of the resected specimen. This situation may be only modestly improved by FDG PET. In current management protocols, a change from N0 to N1 would not result in a change in patient management, but it is associated with a decrease in 5-year survival.

The most important finding from this study is that FDG PET revealed the presence of unsuspected advanced disease (T4 implants in 6 and M1 disease in 24) in 30 (21.1%) of 142 patients. Among the patients without a known history of a treated brain metastasis, unsuspected advanced disease was found in 27 (20%) of 135. In these patients management was altered toward confirmation of advanced stage rather than mediastinal lymph node evaluation, thoracot-

omy, and resection as originally planned. In another 5 (4.2%) of 118 cases, FDG PET revealed lymph node disease at nodal stations that would not have been evaluated by mediastinoscopy. These nodes could then be targeted in a specific diagnostic approach to confirm or exclude N2 or N3 nodal disease, preventing primary resection of locally advanced NSCLC and directing patients toward combined modality therapy. In the other cases in which uptake on FDG PET indicated mediastinal lymph node involvement with tumor, FDG PET provided localizing information used by the thoracic surgeon to target the lymph nodes of highest yield. This was especially critical in cases in which the chest CT did not reveal any evidence of mediastinal lymph node enlargement.

The addition of FDG PET to the diagnostic workup of potentially resectable NSCLC patients provides multiple benefits. The discovery of metastatic disease avoids a non-therapeutic thoracotomy, with its attendant morbidity and mortality, permits the referral of these patients for chemotherapy, and also avoids inefficient and unnecessary surgical staging procedures. PET also may help to improve the accuracy of prethoracotomy mediastinoscopy by identifying lymph nodes that are suspect for metastasis and can be specifically targeted for biopsy. Mediastinoscopy is still useful to confirm the presence of N2 or N3 disease, because PET overstaged the mediastinal lymph nodes in 3 (2.5%) of 118 patients who might have been incorrectly denied surgery with curative intent. The value of routine mediastinoscopy is supported, because PET understaged the mediastinum in 8 (6.8%) of 118 patients, and 7 (87.5%) of 8 of these were detected by mediastinoscopy before thoracotomy, allowing referral for induction therapy before pulmonary resection. Our aggressive prethoracotomy staging with routine FDG PET and mediastinoscopy identified unsuspected distant metastases in 24 of 142 cases, pleural implants in 6 of 142 cases, mediastinal lymph node metastases requiring a specialized approach for biopsy in 5 of 118 cases, and mediastinal lymph node metastases that changed treatment from primary surgery to combined modality therapy in 41 of 42 cases (34 detected by PET plus 7 additional detected by mediastinoscopy). Altogether, there were 35 (24.6%) of 142 cases in which the FDG PET scan revealed disease that would not have been found by conventional staging with bronchoscopy and mediastinoscopy.

Improved accuracy in preoperative staging should provide an improvement in survival by two mechanisms. First, selecting out patients with true stage IIIB and IV disease from those with true stage I or II disease will improve the prognosis of patients with the lower stages by stage migration (the Will Rogers phenomenon).³³ Second, patients whose disease is accurately downstaged are likely to have more aggressive therapy, possible surgical resection, and treatment with curative intent rather than palliative intent.

PET may also benefit the surgeon and patient by directing the lymph node sampling performed as part of a mediastinoscopy. With the advance notice of the presence of a pathologic lymph node by PET, the surgeon will search more aggressively for all nodes at that anatomic station. This results in an improvement of the sensitivity of mediastinoscopy. Moreover, the presence of positive mediastinal lymph node involvement on FDG PET may allow the thoracic surgeon to limit which lymph node stations need to be examined. If PET predicts the presence of N3 disease, all that is needed is to prove a single positive node on that side. However, if PET predicts N2 disease only, one ipsilateral positive node can be harvested but the contralateral side still needs to be thoroughly sampled to exclude microscopic N3 lymph node disease, which PET could have missed.

Many surgeons commonly schedule mediastinoscopy and thoracotomy as a combined procedure. With the high positive predictive value of FDG PET in the mediastinum, one does not need to plan the operating time to include a thoracotomy when PET has predicted positive mediastinal involvement. In instances in which mobilization of mediastinal tissues may be necessary as part of an extensive resection (eg, carinal resection and reconstruction), one may elect to stage the cancer by FDG PET only and plan to perform the mediastinoscopy at the time of the planned resection. This would avoid the development of scarring after a staged mediastinoscopy, which would render the eventual resection technically more difficult. FDG PET may also be substituted for surgical staging in cases in which surgical staging would be contraindicated or less safe. For example, the aortopulmonary window of a patient with a left upper lobe tumor is much more difficult to evaluate before thoracotomy if the patient has had a left internal thoracic artery cardiac graft. Other such scenarios in which a mediastinoscopy could be unsafe would include a patient who has had a laryngectomy and one who has had a mediastinoscopy for a previous lung cancer workup and has a new primary lesion. In these instances, reliance on FDG PET staging may be necessary.

In our experience, the diagnostic accuracy of the PET-enhanced clinical staging is high and far exceeds the accuracy of CT-only staging reported in the literature. Because of its value in assessing the T status and anatomy of a tumor, CT of the thorax remains necessary for initial NSCLC staging. Because of the reported poor accuracy of CT in staging the mediastinum, however, there may no longer be a need for intravenous contrast administration if FDG PET is to be performed as well.

The results for FDG PET accuracy reported in this study are in keeping with those reported in the literature for distant metastatic disease and mediastinal nodal evaluation.^{18-20,32} Although many advocate the use of FDG PET in place of surgical staging, we believe that the two are com-

plementary and allow us to perform a more accurate overall staging, to the benefit of the individual patient. PET has previously been used primarily to screen for lymph node spread and distant metastases, but it also provides localizing information that allows directed and therefore more sensitive surgical staging and refinement of patient selection for curative resection.

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References

- Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. *CA Cancer J Clin*. 1999;49:8-31, 1.
- Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest*. 1997;111:1710-7.
- McCloud TC, Bourgouin PM, Greenberg RW, Kosiuk JP, Templeton PA, Shepard JA, et al. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. *Radiology*. 1992;182:319-23.
- Ettinger DS, Cox JD, Ginsberg RJ, Komaki R, Kris MG, Livingston RB, et al. NCCN Non-Small-Cell Lung Cancer Practice Guidelines. The National Comprehensive Cancer Network. *Oncology (Huntingt)*. 1996;10:81-111.
- Seely JM, Mayo JR, Miller RR, Muller NL. T1 lung cancer: prevalence of mediastinal nodal metastases and diagnostic accuracy of CT. *Radiology*. 1993;186:129-32.
- Specht G, Carlens DB, In Jepson O, Sorenson HR. Mediastinoscopy. Odense, Denmark: Odense University Press; 1971.
- 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.
- 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.
- Coughlin M, Deslauriers J, Beaulieu M, Fournier B, Piroux M, Rouleau J, et al. Role of mediastinoscopy in pretreatment staging of patients with primary lung cancer. *Ann Thorac Surg*. 1985;40:556-60.
- De Leyn P, Schoonooghe P, Deneffe G, Van Raemdonck D, Coosemans W, Vansteenkiste J, et al. Surgery for non-small cell lung cancer with unsuspected metastasis to ipsilateral mediastinal or subcarinal nodes (N2 disease). *Eur J Cardiothorac Surg*. 1996;10:649-54.
- Dillemans B, Deneffe G, Verschakelen J, Decramer M. Value of computed tomography and mediastinoscopy in preoperative evaluation of mediastinal nodes in non-small cell lung cancer: a study of 569 patients. *Eur J Cardiothorac Surg*. 1994;8:37-42.
- Whittlesey D. Prospective computed tomographic scanning in the staging of bronchogenic cancer. *J Thorac Cardiovasc Surg*. 1988;95:876-82.
- Brion JP, Depauw L, Kuhn G, de Fracquen P, Friberg J, Rocmans, et al. Role of computed tomography and mediastinoscopy in preoperative staging of lung carcinoma. *J Comput Assist Tomogr*. 1985;9:480-4.
- Staples CA, Muller NL, Miller RR, Evans KG, Nelems B. Mediastinal nodes in bronchogenic carcinoma: comparison between CT and mediastinoscopy. *Radiology*. 1988;167:367-72.
- Jolly P, Hutchinson C, Detterbeck F, Guyton S, Hofer B, Anderson R. Routine computed tomographic scans, selective mediastinoscopy, and other factors in evaluation of lung cancer. *J Thorac Cardiovasc Surg*. 1991;102:270-1.
- Gdeedo A, Van Schil P, Corthouts B, Van Mieghem F, Van Meerbeek J, Van Marck E. Prospective evaluation of computed tomography and mediastinoscopy in mediastinal lymph node staging. *Eur Respir J*. 1997;10:1547-51.
- Ratto GB, Mereu C, Motta G. The prognostic significance of preoperative assessment of mediastinal lymph nodes in patients with lung cancer. *Chest*. 1988;93:807-13.
- Saunders CA, Dussek JE, O'Doherty MJ, Maissey MN. Evaluation of fluorine-18-fluorodeoxyglucose whole body positron emission tomography imaging in the staging of lung cancer. *Ann Thorac Surg*. 1999;67:790-7.
- Weder W, Schmid RA, Bruchhaus H, Hillinger S, von Schulthess GK, Steinert HC. Detection of extrathoracic metastases by positron emission tomography in lung cancer. *Ann Thorac Surg*. 1998;66:886-92.
- Rao J, Abella-Columna E, Pounds TR, Myers RW, Valk PE. Prevalence of metastatic disease and impact of PET on management in staging lung cancer: a clinical series of 400 patients. *J Nucl Med*. 2000;41 Suppl:75P.
- Bury T, Corhay JL, Paulus P, Weber T, D'Harcour JB, Limet R, et al. [Positron emission tomography in the evaluation of intrathoracic lymphatic extension of non-small cell bronchial cancer: a preliminary study of 30 patients]. *Rev Mal Respir*. 1996;13:281-6.
- Bury T, Dowlati A, Paulus P, Hustinx R, Radermecker M, Rigo P. Staging of non-small-cell lung cancer by whole-body fluorine-18 deoxyglucose positron emission tomography. *Eur J Nucl Med*. 1996;23:204-6.
- Chin R, Ward R, Keyes JW, Choplin RH, Reed JC, Wallenhaupt S, et al. Mediastinal staging of non-small-cell lung cancer with positron emission tomography. *Am J Respir Crit Care Med*. 1995;152:2090-6.
- Guhlmann A, Storck M, Kotzerke J, Moog F, Sunder-Plassmann L, Reske SN. Lymph node staging in non-small cell lung cancer: evaluation by [18F]FDG positron emission tomography (PET). *Thorax*. 1997;52:438-41.
- Gupta NC, Graeber GM, Rogers JS 2nd, Bishop HA. Comparative efficacy of positron emission tomography with FDG and computed tomographic scanning in preoperative staging of non-small cell lung cancer. *Ann Surg*. 1999;229:286-91.
- Patz EF Jr, Lowe VJ, Goodman PC, Herndon J. Thoracic nodal staging with PET imaging with 18FDG in patients with bronchogenic carcinoma. *Chest*. 1995;108:1617-21.
- Sasaki M, Ichiya Y, Kuwabara Y, Akashi Y, Yoshida T, Fukumura T, et al. The usefulness of FDG positron emission tomography for the detection of mediastinal lymph node metastases in patients with non-small cell lung cancer: a comparative study with X-ray computed tomography. *Eur J Nucl Med*. 1996;23:741-7.
- 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.
- Steinert HC, Hauser M, Allemann F, Engel H, Berthold T, von Schulthess GK, et al. Non-small cell lung cancer: nodal staging with FDG PET versus CT with correlative lymph node mapping and sampling. *Radiology*. 1997;202:441-6.
- Valk PE, Pounds TR, Hopkins DM, Haseman MK, Hofer GA, Greiss HB, et al. Staging non-small cell lung cancer by whole-body positron emission tomographic imaging. *Ann Thorac Surg*. 1995;60:1573-81.
- Vansteenkiste JF, Stroobants SG, Dupont PJ, De Leyn PR, De Wever WF, Verbeken EK, et al. FDG-PET scan in potentially operable non-small cell lung cancer: do anatomical PET-CT fusion images improve the localisation of regional lymph node metastases? The Leuven Lung Cancer Group. *Eur J Nucl Med*. 1998;25:1495-501.
- Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s—meta-analytic comparison of PET and CT. *Radiology*. 1999;213:530-6.
- Feinstein A, Sosin D, Wells C. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med*. 1985;312:1604-1608.

Discussion

Dr John Mitchell (Stanford, Calif). Certainly it is hard to take issue with the main premise of this study, that PET aids in the staging of NSCLC. Since the mid 1990s we have all read several reports documenting the superiority of PET scanning to CT in identifying metastatic disease both within the mediastinum and at distant sites. In this study of 144 patients with potentially operable lung cancer, PET identified unsuspected distant metastatic disease

precluding resection in 16% of the patients and was able to correctly differentiate the presence or absence of mediastinal lymph node involvement approximately 90% of the time. Further, use of PET scanning proved helpful in directing subsequent surgical staging efforts and occasionally altered the method of surgical staging used in the patient evaluation. Realizing this, Vesselle and colleagues point out that PET scanning should serve in a complementary, rather than in a mutually exclusive, role with other staging methods such as mediastinoscopy. However, in our current era dominated by the ever-increasing pressure to contain costs, it should be noted that a PET scan, with a price tag in the thousands of dollars, is not an inexpensive test to order. In addition, access to a dedicated PET scanner, although improving, is still not widespread. I am sure that there are still many thoracic surgeons who are still sorting out the exact role that PET scanning should have in the workup of their patients with NSCLC. With that in mind, I have a couple of questions for Dr Vesselle.

First, although you touched on it somewhat in your presentation, I wonder whether you could comment further on how PET is currently used at your institution in the evaluation of patients with lung cancer. For example, do essentially all patients undergo PET scanning, or is the test used at least somewhat selectively on the basis of other imaging studies and the patient's clinical presentation?

Dr Vesselle. FDG PET can serve several roles. The well-established role that we are discussing now is that of staging, but it can be used to restage, to look for sites of disease recurrence, and to affect management. It can be used also to try to improve the prognostic assessment in patients by looking at the level of uptake in the primary tumor, which we did not discuss here. And it can be used to assess response to therapy, and this is done by our chemotherapy colleagues. With regard to using it as a primary staging tool, our colleagues order it pretty much for all the cases that are potentially resectable, because it helps in finding unsuspected advanced disease and in localizing mediastinal disease. We make strong efforts to schedule the cases in a timely fashion, so that the surgeons can have the information provided to them without delaying time to the operating room.

Dr Mitchell. Second, with the high diagnostic accuracy of PET as you have noted in your study, do you believe that it is appropriate to omit mediastinoscopy or other further staging methods if the PET scan is negative for the presence of mediastinal or distant metastatic disease?

Dr Vesselle. This is a point of debate across the country. It depends where one wants to operate in terms of accuracy. If one wants a 98% or 99% accuracy in staging, one cannot omit the surgical staging steps even with a well-performed FDG PET scan. If one is willing to practice at a 90% or 85% accuracy level, I guess these steps could be skipped. Because the chance for a cure for these patients lies in resection, we do not want to deny a resection to a patient because we have overread something. As you know, in PET there are some cases of inflammatory nodes having uptake that could be overread as N2 disease. At the same time, microscopic disease is present, and we sometimes find it but in most cases do not, and it is only found by harvesting the lymph nodes. These patients with microscopic mediastinal disease are the ones that are likely to respond the best to induction therapy. If we just operate on them without detecting this microscopic focus of me-

diastinal disease, they will have tumor recurrence in the mediastinum. I think that the two modalities play complementary roles, and we make every effort to stage these cases as well as possible.

Dr Mitchell. Your comments lead me to my third question, which has to do with the limitations of PET scanning. The sensitivity and specificity of PET are influenced by the inherent metabolic activity of the tumor, the tumor volume, the metabolic activity of the adjacent reactive cells, and the resolution of the PET images. The limitations imposed by these factors were highlighted in your article by the deliberate omission of tumors less than 1 cm in size and by your admitted difficulty in accurately documenting N1 disease. Could you comment further on the impact these limitations had on your study, and on the use of PET scanning in the evaluation of lung cancer in general?

Dr Vesselle. Yes, in this series we only reported on the patients who had primary tumors greater than 1 cm in diameter, and a lot of the tumors were small, between 1 and 2 or 1 and 3 cm. We had a lot of T1 lesions. The reason why the small tumors were omitted is not because we do not perform FDG PET on primary tumors that are less than 1 cm in diameter but rather because this is part of a larger, broader National Institutes of Health-funded trial looking at the prognostic significance of the accumulation of FDG in the primary tumor. To quantitate that properly in the PET scanner, you cannot have a lesion that is too small, because if it is too small relative to the resolution of the machine, there is a blurring that takes place and the way we compute the standard uptake value of the primary tumor gets really error prone as the lesions get very small. This is why our series excluded the very small lesions, but that has no bearing on the accuracy in the mediastinum. There is no relationship that we have found between the size of the primary and the accuracy of PET in the mediastinum at this point.

You wanted to know about the limitations of PET in general. Detectability of a lesion, whether a primary tumor or a mediastinal lymph node, by PET depends on two main factors. One is the intrinsic characteristics of the scanner, its reconstructed resolution from the processing you do of the data, and the other is the metabolic activity of the cells that make up this lesion. For example, although all NSCLCs in general are pretty metabolically active, except for bronchoalveolar cell carcinomas, the cells that make up a node will be hot, and it does not take much tissue for us to be able to detect it. At the other end of the spectrum, a slow-growing tumor such as prostate cancer, for example, does not accumulate much of the FDG tracer, and it may take a centimeter and a half worth of metastatic node before we can detect it by PET. These two factors affect detectability of lesions, but they affect NSCLC, with the exception of bronchoalveolar cell carcinoma which is known to have low metabolic activity, a lot less than some of the tumors with lower metabolic activity.

Dr Frederic Grannis (*Long Beach, Calif*). We are also interested in PET scan as a screening test. I am concerned about one of your comments, that you consider mediastinoscopy to be the criterion standard for detection of N2 metastases. I think that, for example, the discussion from the Marie Lannelongue group, who found 6 patients with N2 disease despite preoperative mediastinoscopy, would suggest that mediastinal lymph node dissection is the criterion standard for the detection of N2 disease. Perhaps I missed it, but did you do systematic mediastinal lymph node dissection in this series?

Dr Vesselle. No, I do not think so, but I think Dr Wood is the best person to answer that question.

Dr Wood. You bring up a topic that you and I have debated at other times. No, we do not do both sampling and lymph node dissection. In the cases that have not had thorough mediastinoscopy and lymph node sampling, we would do a mediastinal lymph node dissection, but we do not do both. As you know, we are doing a trial of that in ACOSOG (American College of Surgeons Oncology Group) to see how much difference there is in mediastinal lymph node dissection versus sampling, both in prognosis and in identifying lymph nodes.

Dr Grannis. That is a good trial, and I think that it will show that the criterion standard is dissection rather than mediastinoscopy. To follow up on the size question, is immunohistochemistry also going to be a criterion standard in the detection of N2 disease?

Dr Vesselle. You are talking about using immunohistochemistry on the sampled nodes, the same way as is done in breast cancer?

Dr Grannis. That is correct.

Dr Vesselle. With regard to the dissection versus mediastinoscopy issue, if you look at the role that PET played in this series in guiding our surgical colleagues in finding the nodes that were positive, it tremendously enhanced the mediastinoscopy yield. In addition, it prompts the surgeon to find disease that would not be

reachable by mediastinoscopy, both pleural implants and nodal stations not reachable by mediastinoscopy. I think that the two modalities together really are synergistic and can improve our surgical staging.

Dr Stephen Swisher (*Houston Tex*). Your article suggested that PET was useful for detecting unsuspected systemic disease but was not very good at identifying N1 or N2 nodes. There were 8 patients who had N2 nodes that were negative with PET but positive at mediastinoscopy. Can you comment a little bit more about these patients? Were they patients with microscopic foci of disease that you could not see on CT?

Dr Vesselle. All these were patients who had no mediastinal disease according to PET or CT, and in all cases there were microscopic foci of disease in the mediastinal nodes. I can recall a couple of patients. One of them had a right upper lobe tumor with a right paratracheal station 4R lymph node, where the disease was found as a really tiny focus at frozen section.

In addition, you mention the lack of detectability of N1 disease. We believe that this is because N1 nodes are small, except when they reach the hilum, and because they are located next to a hot tumor we are not going to see them. These factors put together—their small size and their presence next to a hot metabolic tumor—make it difficult for us to see them on PET. Fortunately, it does not change the overall management.