Accuracy and Cost-Effectiveness of [18F]-2-Fluoro-Deoxy-D-Glucose-Positron Emission Tomography Scan in Potentially Resectable Non-small Cell Lung Cancer*

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Study objectives: This retrospective study of patients who were referred for surgical resection of non-small cell lung cancer (NSCLC) assessed the accuracy and cost-effectiveness of positron emission tomography (PET) with radiolabeled [18F]-2-fluoro-deoxy-D-glucose (FDG) in staging mediastinal lymph nodes (MLNs).

Design: From January 2001 to September 2002, 90 patients with suspected or proven NSCLC who had been referred for curative resection were retrospectively reviewed. All patients were without evidence of metastatic disease. Sixty-nine of the 90 patients had undergone thoracic FDG-PET imaging as part of their evaluation and are the focus of this study. Sensitivity, specificity, accuracy, and positive and negative predictive values for metastasis to the MLN were calculated for CT scanning vs FDG-PET scanning. Four algorithms for staging MLN with mediastinoscopy and/or FDG-PET scan were compared.

Measurements and results: Sixty-nine patients underwent preoperative CT and FDG-PET scans, and 32 of 69 patients underwent mediastinoscopy. Fifty-seven patients underwent thoracotomy with complete mediastinal lymphadenectomy. Sensitivity, specificity, accuracy, and positive and negative predictive values for CT scans and FDG-PET scans were 46%, 86%, 78%, 43%, and 87%, and 62%, 98%, 91%, 89% and 92%, respectively. Mediastinoscopy was accurate in 32 of 32 patients (100%). Routine mediastinoscopy remains the most economically reasonable strategy with excellent sensitivity. Selective FDG-PET imaging improved the sensitivity of noninvasive staging for patients with normal MLNs on CT scans.

Conclusions: Selective use of FDG-PET imaging improves staging accuracy compared to CT scanning alone and makes it a cost-effective adjunct to the preoperative staging of NSCLC. However, in patients with adenocarcinoma and MLNs of < 1 cm, FDG-PET scanning cannot yet replace mediastinoscopy.

Key words: cancer staging; carcinoma; [18F]-2-fluoro-deoxy-D-glucose PET scan; non-small cell lung cancer

Abbreviations: FDG = [18F]-2-fluoro-deoxy-D-glucose; MLN = mediastinal lymph node; NSCLC = non-small cell lung cancer; PET = positron emission tomography

Non-small cell lung cancer (NSCLC) compromises 75 to 80% of all lung cancers currently and is the leading cause of cancer deaths in the United States.1 Bronchogenic carcinoma is estimated to have caused 31.0% and 24.6%, respectively, of all cancer-related deaths in the year 2002 for men and women.2 The optimal treatment of lung cancer relies on proper staging of the disease. The most commonly employed staging system is that of the American Joint Committee on Cancer tumor, node, metastasis description. This staging system is based on tumor size, regional nodal involvement, and the presence or lack of metastasis. Nodal status is a strong predictor of the effectiveness of surgical intervention for lung cancer. N1 nodal status in disease that is limited to the lung parenchyma and

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ipsilateral hilum, and is surgically resectable with intent to cure. N2 nodal status is disease limited to the ipsilateral mediastinum, including the tracheobronchial angle or subcarinal, and is also potentially curative with surgery. This is the target patient population for neoadjuvant therapy protocols, making identification of N2 disease preoperatively particularly critical. Finally, N3 status is disease found in the contralateral mediastinum or scalene/supracarinal lymph nodes and is considered unresectable.

The accurate staging of N2 status has become particularly important as neoadjuvant therapy prior to surgical resection may improve long-term survival in stage IIIA NSCLC patients. Many diagnostic tools have been investigated in the early detection and staging of NSCLC, including chest radiograph, CT imaging, MRI, bronchoscopy, thoracoscopy, and mediastinoscopy. Conventional staging with mediastinoscopy is the most accurate means of staging; however, it is associated with a small, but appreciable, morbidity and mortality.

Positron emission tomography (PET) scanning with radiolabeled \([18F]\)-2-fluoro-deoxy-D-glucose (FDG) imaging has shown substantial promise in the past decade in aiding the noninvasive preoperative staging of lung cancer. FDG-PET imaging uses the radiolabeled FDG tracer as a glucose analog with comparable uptake in metabolically active cells. The positron-labeled molecule is transported into cells via glucose transporters. Once inside the cell, it is phosphorylated by hexokinase and essentially is trapped in the cell. Due to their high proliferation rate, tumor cells have an increased glucose metabolism, a characteristic that is exploited by FDG-PET imaging. FDG-PET imaging has been reported to have superior sensitivity, specificity, and accuracy in the detection of mediastinal nodal involvement compared to those of thoracic CT imaging. It also has proven to be effective in the detection of distant metastases on whole-body imaging, thereby identifying unresectable disease and directing patient management.

The primary purpose of this study was to assess the accuracy of FDG-PET imaging in staging NSCLC in mediastinal lymph nodes (MLNs) in patients who are considered to be appropriate candidates for curative resection. The secondary purpose of the study was to determine a cost-effective utilization of this technology in staging MLNs in NSCLC based on actual numbers from our study population. All patients had undergone extensive preoperative staging, including FDG-PET imaging, prior to referral for surgical resection. Any patient with metastatic disease was excluded from this study and, notably, N3 disease was not diagnosed in any patients by mediastinoscopy. All patients underwent a histologic evaluation of MLNs by mediastinoscopy and/or mediastinal nodal dissection at thoracotomy. We analyzed the sensitivity, specificity, accuracy, and positive and negative predictive values of preoperative FDG-PET imaging and compared them with clinical staging using chest CT scans. Four staging algorithms were developed to compare the accuracy and cost-effectiveness of mediastinoscopy with FDG-PET scanning as a means for the preoperative staging of NSCLC.

Materials and Methods

Patient Selection

Ninety patients with suspected or biopsy-proven NSCLC who were referred for potentially curative resection between January 2001 and September 2002 to the Thoracic Surgery Service at the Minneapolis Veterans Affairs Medical Center were retrospectively reviewed. Patients with evidence of metastatic disease were not included in this study as they are often referred directly to the oncology service. In addition, patients with evidence of metastatic disease who underwent mediastinoscopy for tissue diagnosis only, but were not surgical candidates for resection, were not included in this review. In addition, 21 patients did not undergo FDG-PET imaging as part of their preoperative evaluation and were excluded from the study. Patients with evidence of metastatic disease on FDG-PET scan, chest CT scan, bone scan, or head CT scan were excluded from this study, as were patients who were not appropriate candidates for curative resection based on cardiopulmonary function.

Sixty-nine of the 90 patients had a complete preoperative evaluation that included CT scan, FDG-PET scan, pulmonary function testing, and, if clinically indicated, bone scan and head CT scan. These 69 patients comprised the study population. CT scan determined tumor stage, and both CT scan and FDG-PET scan determined nodal stage preoperatively. Each patient was an appropriate candidate for surgical intervention. At the time of surgical evaluation, the decision was made to proceed with either mediastinoscopy prior to surgical resection of the primary tumor or throracotomy alone. If a mediastinoscopy was performed (34 patients), a frozen section histologic evaluation of the specimens was performed. If N2 disease (ipsilateral metastasis to the MLNs) was present, the patient was considered to be at stage IIIA, and definitive resection was not performed at that time. No patient in this study was found to be stage IIIB. Stage IIIA patients received neoadjuvant chemotherapy, with resection reserved for those patients demonstrating evidence of response to neoadjuvant therapy. Stage I/A/B and II/A/B patients went on to undergo thoracotomy for surgical resection as well as complete MLN lymphadenectomy. A comparison of preoperative staging of the mediastinum using FDG-PET imaging was made to conventional preoperative staging using chest CT scanning, with the accuracy of each study assessed against the pathology results obtained by mediastinoscopy or MLN dissection at the time of thoracotomy. All 69 patients underwent tissue sampling of MLNs to compare to the imaging results.

CT Imaging

All CT examinations were performed at our institution within 6 weeks prior to operation using a helical CT scanner (Lightspeed Plus; General Electric Medical Systems; Knoxville, TN). Images
were obtained from the lung apices to the adrenal glands with 5-mm-thick sections after IV injection of 100 mL contrast medium (Ultrascan; Berlex Laboratories; Montvale, NJ) and were read by a radiologist prior to obtaining a FDG-PET scan. MLNs were considered radiologically suspicious for malignant involvement if they were ˃ 1 cm in their short-axis diameter.

FDG-PET Imaging

FDG (PETNet; Eagan, MN; and Eastern Isotopes; Chicago, IL) was produced, and a mean IV injection of 12 ± 10% mCi was administered 45 to 60 min prior to the positioning of patients onto the PET scanner (ECAT Exact; Siemens; Knoxville, TN). A torso scan (ears down to the bladder/pelvis) was obtained. The transaxial three-dimensional resolution of the scanner at 10 cm is 6.0 mm with a count rate of 180 kilocounts/s/mCi/mL. The attenuated and nonattenuated images were simultaneously displayed on a high-resolution color monitor and were interpreted by a nuclear medicine physician who was not blinded to the chest CT scan results. An FDG-PET scan was considered to be positive in the mediastinum if there was any uptake in the ipsilateral or contralateral MLN that was separate from the primary mass.

Mediastinoscopy

Mediastinoscopy was performed in 34 of the 69 study patients according to the following criteria: (1) presence of ipsilateral or contralateral MLNs with a diameter of ˃ 1.0 cm in the short axis on the chest CT scan; (2) central tumors, even if MLN did not meet the size criteria of ˃ 1.0 cm; (3) MLN uptake seen on FDG-PET scan; and (4) high-risk surgical candidates. Standard cervical mediastinoscopy was performed, with nodal stations 4L, 4R, and 7 being the most commonly sampled. In one patient, lymph node from station 5 were enlarged, so a left anterior mediastinotomy was performed as well when the cervical mediastinoscopy was negative. Patients with clinical stage I or II NSCLC and without the above criteria based on FDG-PET and CT scans did not routinely undergo mediastinoscopy (35 patients), but did have complete MLN lymphadenectomy at the time of thoracotomy.

If at the time of mediastinoscopy, a patient had metastasis of NSCLC to the MLNs, the thoracotomy with lung resection was not performed. Instead, the patient was referred for neoadjuvant chemotherapy. If the MLNs were negative for metastasis, we proceeded immediately to thoracotomy with lung resection and a complete mediastinal lymphadenectomy. All specimens were labeled according to the American Thoracic Society guidelines. Evidence of metastasis to the MLNs by histology was compared to CT imaging and was used to calculate the sensitivity, specificity, accuracy, and positive and negative predictive values of each method.

Cost Comparison

To determine the most economic health-care strategy for our thoracic surgery service, four staging algorithms were designed to compare two conventional staging methods of the mediastinum for NSCLC to those that incorporate FDG-PET imaging results (Fig 1). Two strategies reflect the established standard of care for NSCLC to those that incorporate FDG-PET imaging results. Strategy A, the simplest, includes mediastinoscopy for every patient thought to have surgically resectable disease, as determined by CT scan. Strategy B uses mediastinoscopy selectively, and it is not performed in patients with stage IA or IIA disease (T1N0–1A) based on CT scan. The other two strategies incorporate FDG-PET scanning as a staging method prior to the inclusion of mediastinoscopy. Although the inclusion of an additional test will immediately increase cost, the goal was to assess how this cost is offset by the reduction in the number of invasive procedures required to accurately stage the patient. These two strategies focus on reducing the reliance on mediastinoscopy for staging but do not attempt to replace it. Strategy C involves a routine preoperative FDG-PET scan for all patients, while strategy D uses FDG-PET scans selectively to enhance the accuracy of CT scans in patients who have normal MLNs. Each strategy then was analyzed for accuracy and cost. Using the results that we experienced for staging with CT scanning, FDG-PET scanning, and mediastinoscopy, we used actual numbers to compare strategies.

Cost was determined using direct medical costs based on Medicare reimbursement (Table 1). The cost of including an FDG-PET scan ($2,774) was compared to the cost of mediastinoscopy ($2,172). The overall cost of mediastinoscopy includes frozen section fees, as intraoperative decisions are routinely made on biopsy specimen testing results. In our practice, the number of frozen sections obtained for mediastinoscopy in patients proceeding on to thoracotomy is at least three. For patients with a positive mediastinoscopy finding, fewer specimens often are required. The fee for frozen section was based on Medicare reimbursement rates, with the first specimen costing $63 and subsequent specimens costing an additional $38 per specimen. Using two specimens as an average, the cost of frozen section was $94. Also, the outpatient facility fee was used in the calculation, as, in this setting, patients would be inpatients only if they went on to thoracotomy. Finally, this analysis does not include any additional costs that may be attributed to complications of mediastinoscopy, given the low rate of morbidity and mortality associated with mediastinoscopy.6

Statistical Analysis

Data were analyzed with respect to accurate diagnosis of MLN involvement with metastatic NSCLC. The diagnostic capabilities of the CT scan and FDG-PET scan were determined by calculating the sensitivity, specificity, accuracy, and positive and negative predictive values.

RESULTS

CT Imaging

All 69 patients underwent chest CT scan and FDG-PET scan with results compared to histologic sampling from mediastinoscopy and/or mediastinal lymphadenectomy. The accuracy of CT scans and FDG-PET imaging in preoperative staging is summarized in Table 2. The prevalence of ipsilateral, histologically confirmed mediastinal involvement (ie, stage II A disease) was 19% (13 patients). There were no patients in this study who had N3 disease. Of the 13 patients with N2 disease, CT imaging correctly identified only 6 (46%). Overall, CT imaging correctly identified 54 of 69 patients (78%). Understaging occurred in seven patients (10%), while overstaging occurred in eight patients (11%). CT scan sensitivity, specificity, and positive and negative predictive values were 46%, 86%, 43%, and 87%, respectively. The overall accuracy of CT scanning was 78%.
FDG-PET imaging accurately staged 63 of 69 patients (91%) in our study. Understaging occurred in five patients (7%), two patients with T2 lesions and three patients with T1 lesions. Only one patient was overstaged (1.4%). FDG-PET scanning correctly identified N2 disease in 8 of the 13 patients (62%). In patients with FDG uptake into the mediastinum, the presence of N2 disease in eight of nine positive FDG-PET scans was confirmed by mediastinoscopy, and mediastinoscopy correctly downstaged the one patient with a false-positive FDG-PET scan result. There were three patients with enlarged lymph nodes on CT scan that were negative by FDG-PET scan. However, there were five false-negative FDG-PET scan results in the 13 patients with proven N2 disease. Thus, the sensitivity, specificity, and pos-

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**FIGURE 1.** Decision trees indicating the four strategies analyzed. ● = decision node; ♦ = terminal nodes; Bx = biopsy.
itive and negative predictive values of FDG-PET imaging for N0–2 disease were 62%, 98%, 89%, and 92%, respectively.

Due to the importance of properly identifying patients with stage IIIA disease prior to lung resection, the records of the five patients with FDG-PET scans that were false negative for the MLNs were reviewed. Of the five patients, two had T2 lesions and underwent mediastinoscopy. One patient had adenocarcinoma and was at high risk for complications from resection. Every attempt at accurate staging was thought to be particularly important prior to thoracotomy. The other patient had a central squamous cell tumor, making a distinction of FDG uptake between the primary and the mediastinum unreliable. Both patients were accurately staged as having stage IIIA disease, with mediastinoscopies diagnosing a positive station 7 lymph node, and the patients were referred for neoadjuvant therapy. The other three patients all had T1 lesions and did not undergo mediastinoscopy. They underwent surgical resection with complete mediastinal lymphadenectomy. All were found to have stage T1 adenocarcinoma with one nodal station positive for metastatic disease.

In addition to the clinical records, the FDG-PET imaging records of these five patients were thoroughly reviewed, as four of the negative studies occurred as a cluster from January 2002 to April 2002. Although all of the patients had uptake of FDG in the primary lung lesion, there was no mediastinal uptake in the lymph nodes that had been determined to be positive by mediastinoscopy or mediastinal nodal dissection. On review of the FDG-PET scan imaging records, there was no discernible difference in the dose or preparation of the FDG, the scanner protocol, the type of scanner, the patient glucose levels, or the timing of the scan to the administration of FDG. All MLNs involved were < 1.0 cm, as determined by CT scan, which may be below the threshold resolution of FDG-PET imaging.

Mediastinoscopy was performed selectively with 34 of the 69 study patients undergoing the procedure. Mediastinoscopy was negative for metastatic disease in 21 patients who then went on to thoracotomy with resection and mediastinal nodal dissection at the same setting. Three patients received a definitive diagnosis of an inflammatory process and did not undergo a thoracotomy. Ten of thirty-four patients had stage N2 disease diagnosed by mediastinoscopy. There were no patients diagnosed with N3 disease in our study. Mediastinoscopy was 100% accurate, as the results of the positive frozen sections were confirmed by final pathology, and the results of the negative mediastinoscopy findings were confirmed by complete lymphadenectomy that was performed at the time of the thoracotomy.

The final histologic diagnoses of the 69 patients are listed in Table 3. Of the 62 patients with a malignancy, all had FDG uptake in the primary lung mass, which corresponded to the CT scan lesion. Seven patients were found to have benign pathology. Surgery was recommended based on the CT scan findings that suggested a malignant appearance or increasing size of the lung mass (seven patients) and associated mediastinal adenopathy (four patients), even though the FDG-PET scan finding was negative in both the primary mass and the mediastinum.
in all seven patients. Histoplasmosis was diagnosed definitively in three patients by mediastinoscopy. Four patients underwent wedge resection of the lung mass to confirm the diagnosis of histoplasmosis (2) and hamartoma (2).

Cost Comparison

We analyzed the costs of the four different staging strategies outlined in Figure 1 using the results of our patient population. In light of the accuracy and sensitivity of each algorithm to correctly stage patients prior to surgical resection, we considered the most reasonable treatment plan in terms of cost and clinical relevancy. The costs of FDG-PET scans and mediastinoscopy were determined by direct Medicare reimbursement based on CPT codes (Table 1). These estimates are very conservative, yet they allow for a standardized cost comparison that would be applicable to other institutions.15

In strategy A (Fig 2), mediastinoscopy would have been performed for all 69 patients with suspected or proven NSCLC. The cost would be $149,868. This is the “gold standard” for staging the mediastinum, and contributes visual and histologic confirmation of the extent of disease. In our 34 patients who had mediastinoscopy, the correct diagnosis was made in all patients. In addition, two of the three patients who were understaged by FDG-PET scan would have most likely been accurately staged by mediastinoscopy as the nodal stations (4R and 7) were accessible. In one patient, the mediastinal nodal station involved was station 5, and this would have been missed by routine mediastinoscopy. Based on our study, routine mediastinoscopy (strategy A) was the most accurate strategy and had a reasonable expense. However, reliance on an invasive staging method for all patients continues to be less appealing.

In strategy B (Fig 3), mediastinoscopy would have been used only in patients with enlarged MLNs (ie, those > 1 cm on the short axis) or in primary lesions greater than T1. For our study population, there were 32 patients with T1 lesions and normal MLNs on CT scans. This selective use of mediastinoscopy would have resulted in 37 patients having mediastinoscopy for a cost of $80,364. However, with an overall sensitivity of 46% for CT scan alone, seven patients overall were understaged. Of these seven patients, four patients had T1 adenocarcinoma lesions, resulting in 4 of 32 patients (13%) being understaged with this strategy. This strategy lowers the cost but does so by reducing the accuracy of the staging. It is a strategy that would have denied neoadjuvant therapy options to 4 of the 13 patients with unsuspected but advanced-stage NSCLC.

In strategy C (Fig 4), an FDG-PET scan would be obtained for all patients, and mediastinoscopy would be performed in the event of a positive CT scan and/or FDG-PET scan finding. In this algorithm, 23 patients had a positive CT scan finding, positive FDG-PET scan finding, or both, and underwent mediastinoscopy. Both of those patients with a positive CT scan finding and a positive FDG-PET scan finding are included in an effort to reduce the false-negative rate. The cost now includes FDG-PET scanning for all 69 patients as well as mediastinoscopy for 23 patients. The total cost would be $241,362. However, there were still four false-negative results in 13 patients with N2 disease. If the criteria of mediastinoscopy for any primary lesion greater than T1 also was included, then only three patients would have been understaged, but the number of mediastinoscopies would be increased as well. This strategy would result in even greater expense than routine mediastinoscopy and remains less accurate.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Mediastinum Correctly Staged by PET Scan</th>
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<tr>
<td>Adenocarcinoma (n = 26)</td>
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<tr>
<td>Squamous cell (n = 24)</td>
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<tr>
<td>Large cell (n = 5)</td>
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<tr>
<td>Benign (n = 7)</td>
<td>7</td>
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<tr>
<td>Combination* (n = 3)</td>
<td>3</td>
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*Three patients were histologically described as having a combination of types (adenocarcinoma/large cell, large cell/neuroendocrine, and adenocarcinoma/squamous cell).

Table 3—Patient Pathologic Data

Figure 2. All patients with resectable NSCLC undergo routine mediastinoscopy.
Strategy B

In strategy D (Fig 5), FDG-PET scanning is used selectively for patients with a CT scan that has normal-sized MLNs and a T1 lesion. This reduces the redundancy of imaging by relying on FDG-PET scanning to detect metastasis to normal-sized MLNs in patients with T1N0–1 lesions, which is a limitation of CT scanning, and continues to rely on mediastinoscopy to confirm metastasis in enlarged MLNs or advanced tumor stage lesions prior to committing the patient to receive neoadjuvant therapy. Mediastinoscopies would be performed if the CT scan findings, FDG-PET scan findings, or both were positive. This strategy reduces the number of FDG-PET scans to 32 and would still require 40 mediastinoscopies. The cost for this strategy in this study group would be \((32 \times \$2,774) + (40 \times \$2,172) = \$175,648\). This strategy lowers the cost of FDG-PET imaging (37 fewer scans) compared to strategy C and results in fewer (19 less) mediastinoscopy procedures than strategy A. This lowers the cost of staging the patient with a routine FDG-PET scan (strategy C), reduces the number of invasive procedures compared to strategy A, and improves the noninvasive staging sensitivity compared to that for CT scan alone.

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Strategy C

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**Discussion**

In a review of the literature that relies on CT scanning for clinical staging, the prevalence of con-
trilateral or ipsilateral mediastinal metastatic disease (N2 or N3) in patients with histologic diagnosis of NSCLC who are being considered for thoracotomy is estimated at 31% (range, 28 to 38%). The objective of FDG-PET scanning in the clinical staging of the mediastinum is to reduce the need for invasive staging methods while improving the sensitivity and specificity compared to CT scanning. A report by Gupta et al demonstrated sensitivity and specificity values of 68% and 61%, respectively, for CT scanning, while FDG-PET scanning had a sensitivity and specificity of 87% and 91%, respectively. They also described correct MLN staging by FDG-PET scans in 15 of 17 lymph nodes that previously had not been detected on CT scan, showing that FDG-PET imaging was more sensitive in detecting early metastasis due to its ability to detect increased tumor metabolism in normal-sized lymph nodes seen on CT scans.

Other reports that focused on mediastinal staging using FDG-PET scanning found only a slight sensitivity advantage over CT scanning alone. Weng et al described sensitivity and specificity values of 73% and 77%, respectively, for CT scanning, and 73% and 94%, respectively, for FDG-PET imaging. Poncelet et al reported similar results for both CT scanning (sensitivity, 55%; specificity, 68%) and FDG-PET scanning (sensitivity, 67%; specificity, 85%). However, because N3 patients were not included in this study, it may represent a highly selected group of patients. Both studies suggested that the lower-than-expected sensitivity of FDG-PET scan limits the reliability of the node-negative scan finding. In an effort to improve the accuracy of FDG-PET scanning, Weng et al reported that the combined use of imaging modalities that contribute complementary information resulted in improved sensitivity, specificity, and overall accuracy (82%, 96%, and 91%, respectively), suggesting that this strategy provided the most accurate staging of mediastinal disease.

Our study used FDG-PET scanning in addition to CT scanning for the clinical staging of NSCLC in 69 patients in an effort to improve the preoperative identification of N2 disease. We did not use the fusion of CT/FDG-PET scanning to try to enhance lymph node detection, but the nuclear medicine physician was not blinded to the results of the CT scan. With the availability of FDG-PET scanning, we adopted a strategy of routine FDG-PET scan (strategy C) for all patients who were referred for surgical resection of NSCLC, yet we continued to rely on liberal indications for mediastinoscopy as our standard policy has been routine mediastinoscopy. We found the sensitivity of FDG-PET imaging to be much lower (62%) than that reported in the literature.
ture, particularly in patients with adenocarcinoma. Four of five patients with a false-negative finding of an FDG-PET scan of the mediastinum had adenocarcinoma as the cell type (Table 3), with a primary mass size of T1 in three patients and T2 in one patient. Our study found that this lack of sensitivity to FDG uptake in normal-sized MLNs in patients with adenocarcinoma to be the greatest limitation of FDG-PET imaging. However, if FDG-PET scan results were combined with CT scan results, the sensitivity, specificity, and overall accuracy (70%, 98%, and 91%, respectively) of clinical staging improved. Of note, in our patient population, the false-positive rate was very low. The likely reason for this difference, as ascertained from other reports, is that our Veterans Affairs Medical Center patient population is a very high-risk group for lung cancer, given the prevalence of older male patients with a significant smoking history.

Prior to FDG-PET imaging availability, two possible strategies with mediastinoscopy were employed clinically that use either routine or selective mediastinoscopy as a staging tool. Mediastinoscopy offers visualization as well as histologic diagnosis, but is an invasive procedure with a small but definitive morbidity.20 The use of routine mediastinoscopy (strategy A) involves performing mediastinoscopy on all patients thought to be candidates for surgical resection. Two strategies were considered, either routine use of mediastinoscopy (strategy B), a patient with T1 NSCLC and normal-sized MLNs seen on a CT scan would not undergo mediastinoscopy. Instead, based on CT scan results for staging the MLN, the patient would proceed directly to thoracotomy, with mediastinal nodal dissection performed at the time of lung resection. Although this strategy eliminates an invasive procedure, it would miss N2 and N3 disease in approximately 10% of the patients.22,23

The availability of FDG-PET imaging allowed us to explore our options for staging the mediastinum in patients with NSCLC, and two strategies were considered that incorporated FDG-PET imaging. Previous reports24 have suggested a cost and sensitivity for FDG-PET imaging that is comparable to mediastinoscopy. Although there is an additional cost in preoperative staging, the reported sensitivity of the test prompted us to consider it as a possible alternative to mediastinoscopy. Two strategies were considered, either routine use of FDG-PET scanning (strategy C) or selective use of FDG-PET scanning (strategy D). Routine FDG-PET imaging (strategy C) in all patients who are surgical candidates for resection includes mediastinoscopy only if both CT and FDG-PET scan results are positive. Had the sensitivity for our study been greater, the need for mediastinoscopy would be reevaluated. Strategy D uses the FDG-PET scan selectively and only in patients with CT scans that reveal T1 lesions with normal-sized MLNs. In this strategy, mediastinoscopy is performed only if the CT scan, the PET scan, or both are positive for the MLNs or reveal advanced T stage disease. Strategy D eliminates the use of FDG-PET scanning if the mediastinal nodes are enlarged on a CT scan, as these patients are likely to undergo mediastinoscopy regardless of the FDG-PET results. An unexpected result of incorporating preoperative routine FDG-PET imaging of the thoracic area may have been the improved diagnosis of metastatic disease in patients with N3 disease. As we did not have any patients in whom N3 disease was diagnosed by mediastinoscopy, it is possible that synchronous extranodal metastases were identified in these patients prior to referral to a surgical service, and so were not included in this study.

The cost-effectiveness of including FDG-PET scanning for staging of the mediastinum in NSCLC patients remains unclear. Prior to the availability of FDG-PET scanning, early-stage NSCLC was staged either with CT scan alone or CT scan plus mediastinoscopy. The decision to use routine mediastinoscopy in what appeared to be early-stage NSCLC is based on the effort to accurately identify patients with N2 disease who would benefit from neoadjuvant therapy. The sensitivity of 99% and specificity of 100% for lymph nodes accessible by mediastinoscopy, as reported by Hamound et al,6 was a marked improvement over the staging capability of CT scanning alone. However, mediastinoscopy is an invasive procedure, with increased costs associated with operative time, pathologic analysis of specimens, and potential morbidity and mortality. Had FDG-PET imaging clearly improved early staging of the mediastinum and replaced mediastinoscopy, its cost-effectiveness would be obvious. The subset of patients who may have a cost-effective benefit from FDG-PET scan staging of the mediastinum are those without adenocarcinoma, as determined by tissue diagnosis prior to surgery. These patients had excellent staging of the mediastinum with FDG-PET scanning with an accuracy of 98% (42 of 43 patients). However, patients often do not receive a tissue diagnosis prior to surgery, making this a limitation of the cost-effectiveness.

A study by Scott et al15 reviewed several strategies for clinical staging of NSCLC. They concluded that of several PET-based strategies, a strategy that included thoracic PET scanning performed only after a negative CT scan finding had the lowest cost with the greatest benefit of additional information. Our results support this use of FDG-PET scanning as a
reasonable adjunct to thoracic CT for preoperative staging of the mediastinum, but we recognize that it has a lower sensitivity compared to routine mediastinoscopy. Using Medicare-based reimbursement rates, outpatient mediastinoscopy remains less expensive than FDG-PET imaging. Although initial studies of FDG-PET scanning suggested that the improvement in sensitivity would make it the ideal noninvasive method with which to stage early-stage NSCLC, this report and other more recent studies\(^\text{10,19}\) that focused on N0-2 disease are less convincing.

Strategy B, the strategy with the lowest cost (no FDG-PET scan, and no mediastinoscopy in patients determined to have stage IA disease by chest CT scan alone), accepts the potential understaging of patients with N2 disease. The most accurate staging strategy (strategy A) remains routine mediastinoscopy in all patients undergoing surgical resection for NSCLC, yet clearly it has the greatest risk.\(^8\) The strategy using the routine addition of FDG-PET scan (solely to stage the mediastinum; strategy C) results in increased cost without improvement in staging accuracy, although this report does not take into account any potential advantage of identifying metastatic disease. Currently, although routine mediastinoscopy has the best staging accuracy, selective FDG-PET scanning (strategy D) improves the sensitivity and specificity of CT scan staging, and does so at a reasonable cost and risk.

In conclusion, the utility of FDG-PET imaging in staging the mediastinum for N0-2 disease remains unclear. In particular, in patients with MLNs of < 1 cm seen on CT scans, FDG-PET scans may under-stage patients who may benefit from neoadjuvant therapy. Although the prognosis for patients with single-station N2 nodal station involvement at the time of resection is reasonable, these patients are still candidates for neoadjuvant therapy. So, although FDG-PET imaging improves noninvasive staging when compared to chest CT scanning, it does not replace the role of mediastinoscopy. A cost-effective strategy that requires the acknowledgment of this limitation would use both selective FDG-PET scanning and selective mediastinoscopy. This is a reasonable, safe, and cost-effective algorithm for staging the mediastinum in patients with NSCLC. A prospective study of the role of FDG-PET scanning in NSCLC staging is indicated to validate this approach.

REFERENCES


