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Frank C. Detterbeck, Steven Falen, M. Patricia Rivera, Jan S. Halle and Mark A. Socinski

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# Seeking a Home for a PET, Part 2\*

## Defining the Appropriate Place for Positron Emission Tomography Imaging in the Staging of Patients With Suspected Lung Cancer

Frank C. Detterbeck, MD, FCCP; Steven Falen, MD, PhD;  
M. Patricia Rivera, MD, FCCP; Jan S. Halle, MD; and  
Mark A. Socinski, MD, FCCP†

In patients who have a high likelihood of having lung cancer, there is little role for positron emission tomography (PET) imaging for diagnosis of the primary lesion. The primary impact of PET imaging is in extrathoracic staging, but it should not replace a clinical evaluation by a physician experienced in lung cancer. PET imaging is most useful for confirmation of the presumed extrathoracic stage in patients with intermediate stages of lung cancer. The role of PET imaging is limited in patients with strong clinical signs of metastatic disease, or in patients with a clinical stage I lung cancer and a negative clinical evaluation. With regard to intrathoracic staging, PET imaging has a definite role in communities in which mediastinoscopy is not available, whereas the impact is limited in institutions in which invasive mediastinal staging is available. The data suggest that a positive PET result in the mediastinum should be confirmed by biopsy. A mediastinoscopy is also reasonable in patients with clinical stage III lung cancer who have no mediastinal PET uptake. It is unclear and controversial whether a biopsy is needed in patients with clinical stage II lung cancer who have no PET uptake in the mediastinum.

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**Key words:** lung cancer; positron emission tomography; staging

**Abbreviations:** cI = clinical stage I; cI,II = clinical stage I,II; cII = clinical stage II; cIII = clinical stage III; cIV = clinical stage IV; FDG = 2-fluoro-2-deoxy-D-glucose; FN = false-negative; FP = false-positive; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PLUS = PET in Lung Cancer Staging; SCLC = small cell lung cancer; TTNA = transthoracic needle aspiration

Positron emission tomography (PET) imaging can be useful in predicting the diagnosis of pulmonary nodules as well as the stage of patients with lung cancer. The approach to a patient with a pulmonary nodule or mass begins with an assessment of the symptoms and risk factors for lung cancer, a review

of sequential chest radiographs, and an examination of the chest CT scan. This allows an estimation to be made of the likelihood that the lesion is a lung cancer. In patients who have a high likelihood of cancer, there is little role for PET for diagnosis. Although PET might make the likelihood of lung

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cancer even higher by intense uptake, the need to obtain a tissue diagnosis in most cases will render this aspect of a PET scan superfluous. Moreover, if a PET study finding was negative, it is likely that most physicians would be uncomfortable trusting this result in the face of highly suggestive clinical and radiographic features. The role of PET for the diagnosis of pulmonary nodules is discussed in more detail in Part 1 of this review.<sup>1</sup>

The major issue in patients with a suspected or proven lung cancer is definition of the extent of disease (staging). The initial clinical evaluation of the

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\*From the Division of Cardiothoracic Surgery, Department of Surgery (Dr. Detterbeck); Department of Radiology (Dr. Falen); Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine (Dr. Rivera); Department of Radiation Oncology (Dr. Halle); and Division of Medical Oncology, Department of Internal Medicine (Dr. Socinski), University of North Carolina at Chapel Hill, Chapel Hill, NC.

†Members of the Multidisciplinary Thoracic Oncology Program, University of North Carolina, Chapel Hill, NC.  
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Correspondence to: Frank C. Detterbeck, MD, FCCP, Division of Cardiothoracic Surgery, Medical School Wing C, Room 354 CB# 7065, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7065; e-mail: [fdetter@med.unc.edu](mailto:fdetter@med.unc.edu)

patient provides a presumptive stage, although this may need to be confirmed by further tests. Although PET imaging is approved in the United States for staging of patients with lung cancer, there is confusion about the appropriate place of PET imaging among the array of available staging tests. Furthermore, there is controversy about whether PET imaging can obviate the need for invasive tests such as mediastinoscopy. Finally, it must be remembered that, in many instances, an invasive test is needed in order to provide confirmation of the diagnosis, completely aside from any staging considerations. This article reviews the data regarding the role of PET imaging in the extrathoracic and intrathoracic staging of patients with lung cancer.

## BACKGROUND

### *General Results of PET for Staging*

Many studies<sup>2-5</sup> have shown that PET is more accurate than CT for the staging of non-small cell lung cancer (NSCLC). A tabulated summary<sup>2</sup> of 2-fluoro-2-deoxy-D-glucose (FDG) PET literature in lung cancer from 1993 through June 2000 showed that for staging of the mediastinum, the average sensitivity and specificity of PET are 83% and 91%, respectively, vs 64% and 74% for CT. A meta-analysis<sup>6</sup> also found an average sensitivity and specificity for PET of 79% and 91%, respectively, as opposed to 60% and 77% for CT. In another study,<sup>7</sup> 10% of 153 patients with NSCLC were downstaged and 33% were upstaged after PET as compared with staging by CT and bone scan. Furthermore, two decision-tree sensitivity analyses<sup>8,9</sup> have suggested that a PET-based strategy for staging of NSCLC is an economically reasonable approach compared with CT alone.

The studies comparing staging of the mediastinum by CT and PET with staging by CT alone, however, are flawed in that staging by CT alone is well known to be inaccurate. Among patients with discrete enlarged lymph nodes, 40% do not have malignant involvement, whereas an average of 15% of patients with normal nodes by CT scan do have N2,3 involvement.<sup>10</sup> Therefore, optimal conventional staging should include mediastinoscopy or some other means of mediastinal node biopsy, at least for the subgroups of patients in whom CT is known to be inaccurate. Furthermore, extrathoracic metastases are present in some patients. Appropriate staging should include a clinical evaluation by a physician who is experienced in the signs and symptoms of distant metastases as well as imaging for distant metastases in subgroups of patients despite the absence of symptoms. PET should not be a substi-

tute for a careful evaluation of the patient by a knowledgeable clinician. Staging by CT alone represents the absence of such clinical input.

The results of a prospective randomized study<sup>11</sup> (known as the PET in Lung Cancer Staging [PLUS] trial) have been published in which conventional workup was compared with conventional workup plus PET in 188 patients who were thought by the primary care physician to be "potentially resectable." The major end point in this study<sup>11</sup> was the rate of futile thoracotomy, which was defined as a thoracotomy without resection, a thoracotomy in patients who were found to have N2 or N3 involvement, or any recurrence or any death occurring within a year of surgery. Patients randomized to staging that included PET imaging had a significantly lower rate of futile thoracotomy (21% vs 41%,  $p = 0.003$ ). The difference in outcomes between the two study arms is due both to a higher rate of recurrence within 1 year (18% vs 6% of operated patients), and the frequent lack of identification of N2,3 involvement prior to thoracotomy in the conventional staging cohort. The overall incidence of N2,3 disease was similar in the two study arms (23% and 26%), but in the conventional staging arm this involvement was established prior to resection in the minority (45%), whereas it was found prior to resection in 75% in the PET staging arm.

A closer look at the PLUS study<sup>11</sup> suggests that it really compares staging with PET to very minimal staging. Conventional workup is vaguely defined as being consistent with the local routine. The patients underwent relatively few staging investigations, either by the primary care physician or the surgeon. Only 3% had a brain CT or MRI, and only 27% a bone scan, despite the fact that the patients had relatively extensive tumors (24% had clinical stage IIIA,B disease). Furthermore, the clinical evaluation appears to have been rather limited. Weight loss was present in 15% of patients, and 9% had a poor performance status. These characteristics are generally viewed as signs of distant metastases, yet the patients were considered to be potentially resectable. This is likely to be the explanation for the high rate of recurrence within 1 year in this study,<sup>11</sup> particularly in the conventional staging group. Thus, it is not clear that the results of the PLUS study<sup>11</sup> can be generalized to patients who undergo a careful clinical evaluation in conjunction with additional studies to confirm the stage when the reliability of the initial stage is known to be poor.

Should all patients with a high likelihood of lung cancer undergo PET imaging? PET can certainly be useful in many instances. However, PET imaging should not be used as a substitute for a clinical evaluation of the patient by a physician. Further-

more, it must be remembered that a PET can also be a nuisance, *eg*, if it frequently draws attention to “noise” and creates a lot of commotion about things that are unimportant in the final analysis. This is especially true in settings where the incidence of actual worrisome events is very low. Therefore, it is best to consider specific patient groups as defined by the presumed cell type and stage in order to achieve a thoughtful integration of PET imaging into the workup of patients with a high likelihood of lung cancer. Before discussing how to incorporate PET imaging, though, it is worth reviewing the data behind the traditional approach to staging of patients with lung cancer.

### *Traditional Approach to Staging in Patients With Probable Lung Cancer*

In many patients, a presumptive diagnosis of lung cancer can be made with a high degree of confidence on the basis of the patient’s age, risk factors, and the radiographic appearance of the tumor. In fact, it is often possible to predict whether the tumor is more likely to be small cell lung cancer (SCLC) or NSCLC (*eg*, rapid growth and marked mediastinal adenopathy without a peripheral lung lesion is typical of SCLC). Although tissue confirmation of malignancy and of the cell type must be obtained at some point, the diagnosis is generally secure enough that it is best to consider the presumptive stage and possible treatment options first. Often an approach can be identified that will establish both a cytologic diagnosis and provide confirmation of the presumptive stage as well (Table 1). Furthermore, the treatment approach may influence how confirmation of the diagnosis is obtained (*eg*, a preoperative diagnosis is not needed if the treatment will be surgical resection). Therefore, the most efficient approach to confirming the diagnosis depends on the presumed cell type, the presumed stage, and the tentatively planned treatment.

The clinical evaluation of patients with a high suspicion of having lung cancer provides a fair amount of information regarding a presumptive clinical stage. However, in many instances the presumed clinical stage is not reliable, and must be confirmed through further testing. The major issues are whether distant metastases are present or not (extrathoracic stage), and whether mediastinal lymph nodes are involved or not (intrathoracic stage).

Signs and symptoms of systemic metastases (*eg*, fatigue, weight loss, poor appetite, neurologic signs and symptoms, bone pain) must be verified because such a positive clinical evaluation carries a substantial false-positive (FP) rate.<sup>12,13</sup> Generally, this has been accomplished by a series of imaging tests such as a brain CT or MRI, a bone scan, and an abdominal CT. In some instances, however, a simple test such as a plain skeletal radiograph of a symptomatic area is definitive enough. When the symptoms and radiographic findings are typical of metastases at multiple sites, most physicians consider this adequate proof of systemic disease without further confirmation. If only a solitary metastatic site is present, tissue confirmation at this site is usually required because the suspected metastatic lesion is not cancer in approximately 10 to 15% of patients.<sup>12,14,15</sup>

In patients with NSCLC and a negative clinical evaluation for the presence of distant metastases, there is controversy about the need to confirm this with additional tests. Most medical and radiation oncologists believe that such confirmation is required, whereas most surgeons do not. A more detailed look at the false-negative (FN) rate of the clinical evaluation suggests an explanation for the discrepancy in these viewpoints. In patients with stage I and II NSCLC, a negative clinical evaluation carries a FN rate of approximately 5%, as has been shown consistently in several studies<sup>12,16,17</sup> using different approaches to this issue. However, in patients with clinical stage III (cIII) NSCLC, the FN

**Table 1—Traditional Approach to Confirmation of the Diagnosis and Stage of Patients With Probable Lung Cancer**

Clinical Scenario	Confirmation of Extrathoracic Stage	Confirmation of Intrathoracic Stage	Confirmation of Diagnosis
SCLC	Radiographic*	Not applicable	Easiest site†
NSCLC			
cIV, multiple typical metastases	Radiographic*	Not applicable	Easiest site†
cIV, solitary potential metastasis	Biopsy of suspected site	Not applicable	Biopsy of suspected site
cIII, diffuse mediastinal infiltration	Radiographic*	Radiographic	Easiest site†
cIII, discrete node enlargement	Radiographic*	Mediastinal node biopsy	Mediastinal node biopsy
cII, cI central or adenocarcinoma	Clinical	Mediastinoscopy	Surgical resection
cI, peripheral	Clinical	Intraoperative node biopsy	Surgical resection

\**eg*, bone scan, abdominal CT, brain CT, or MRI.

†*eg*, sputum, bronchoscopy, fine-needle aspiration of supraclavicular node, TTNA.

rate of a clinical evaluation is approximately 15 to 30%.<sup>12,13,17</sup> It must be stressed, however, that the clinical evaluation must be carefully done, and it has been demonstrated that there should be a low threshold to investigation of subtle symptoms.<sup>18</sup> The additional investigation for possible asymptomatic distant disease has traditionally involved a head CT or MRI and a bone scan (and imaging of the liver and adrenals if this was not included with the chest CT).

If no systemic metastases are found in patients with NSCLC, the status of the mediastinum becomes a crucial issue. Most physicians do not obtain further confirmation when there is extensive infiltration of the mediastinum to the point where discrete lymph nodes can no longer be discerned. Although there are no data that clearly define this, clinical practice suggests that this approach is justified. However, when there is enlargement of discrete lymph nodes, confirmation of the true status of the nodes is necessary, because there are extensive data that in approximately 40% of patients there is no mediastinal involvement despite the radiographic appearance.<sup>10,19,20</sup> Conversely, although a chest CT may suggest no mediastinal node involvement (all nodes are < 1 cm in short axis), approximately 15% of patients will be found to have nodal involvement.<sup>10,19,20</sup> The FN rate of a negative chest CT finding for the mediastinum is particularly high (20 to 25%) in the case of a central tumor, an adenocarcinoma, or if there is evidence of N1 node enlargement.<sup>10,20</sup> Therefore, the clinical stage of the mediastinum as defined by CT alone is notoriously inaccurate in a variety of settings, and further confirmation of the clinical stage is desirable. Traditionally this has been accomplished by invasive procedures such as mediastinoscopy, transbronchial needle aspiration, or esophageal ultrasound and needle aspiration.

#### ROLE OF PET FOR STAGING IN PATIENTS WITH LUNG CANCER

##### *Role of PET in Patients With Probable SCLC*

Patients with SCLC generally have a characteristic presentation and radiographic appearance. Because mediastinal involvement and often systemic disease is so prevalent, it is widely accepted to rely on radiographic staging alone (bone, brain, chest, and abdominal imaging) without further confirmation of the stage. Proof of the diagnosis of SCLC is generally obtained from whatever site and method is easiest. This may involve sputum analysis, bronchoscopy, needle aspiration of a supraclavicular node or a pleural effusion, or transthoracic needle aspiration (TTNA) of mediastinal tumor. Unless there are

atypical features of the patient's presentation, the pattern of mediastinal or systemic involvement, or the clinical course, there is no need for additional confirmation of the diagnosis or stage in patients with SCLC.

It is unclear how PET imaging should best be integrated into the workup of patients with SCLC. A PET scan is likely to show systemic metastatic sites at least as well as CT or MRI scans of the bones, chest, and abdomen, although a brain CT or MRI is still likely to be necessary. While PET imaging currently remains a relatively expensive test, it is no more costly than multiple other scans. This would argue that PET imaging may be a reasonable alternative to multiple scans in most patients with SCLC. However, there are few data as yet to help with the decision regarding the role of PET imaging in the workup of patients with SCLC.<sup>21,22</sup>

##### *Probable NSCLC With Symptoms of Systemic Metastases*

Some patients present with signs and symptoms of obvious advanced disease. For example, this may include patients with subcutaneous metastatic deposits, patients with symptoms and plain skeletal radiographs demonstrating metastases, or patients with palpable supraclavicular node enlargement or a large pleural effusion. Although these latter two examples only signify cIIIB disease, these patients have a poor prognosis and are treated the same as patients with clinical stage IV (cIV) NSCLC. There is little reason to obtain a PET scan in patients with such obvious advanced disease. A needle aspiration of one of the sites of involvement will yield a tissue diagnosis and prove the advanced nature of the disease without the expense of PET imaging.

Other patients present with more subtle signs of possible systemic disease, particularly constitutional symptoms such as fatigue, anorexia, or weight loss. Further investigation to find possible metastatic disease is warranted, given that the clinical evaluation for systemic metastases has a high FP rate.<sup>12</sup> A PET scan is a reasonable alternative to a battery of other imaging studies. However, it must be realized that there are also many indeterminate findings on PET imaging that may require a battery of additional studies or interventions. Nevertheless, the data demonstrate that PET is more accurate than conventional imaging. In a study<sup>5</sup> of 100 patients with lung cancer, PET imaging for distant metastases had a sensitivity of 91%, a specificity of 96%, a FP rate of 5%, and a FN rate of 7%. In contrast, conventional imaging was found to have a sensitivity of 80%, a specificity of 80%, a FP rate of 24%, and a FN rate of 17%.<sup>5</sup> Furthermore, PET is more reliable when

compared specifically with a radionuclide bone scan. The sensitivity of PET imaging for detecting bone metastases is 90 to 92%, the specificity is 98%, the FN rate is 1 to 2%, and the FP rate is 8 to 10%,<sup>5,23</sup> as opposed to an average sensitivity of 76%, specificity of 69%, FP rate of 63%, and FN rate of 9% for bone scanning in patients with lung cancer.<sup>12</sup> Thus, the ability of PET to detect distant metastases is high, and the interpretation of a positive or negative PET result in an individual patient can be made with relative confidence. However, conventional imaging of the brain is still required, because the high glucose metabolism of the brain makes FDG-PET a poor imaging test in this organ.

PET imaging is particularly useful in patients with an atypical presentation, a solitary site of metastasis, or with lesions that are indeterminate on other scans. For example, patients may present with an enlarged adrenal gland, an indeterminate liver lesion, or a second pulmonary nodule. The FN rate of PET imaging in adrenal lesions is close to zero,<sup>5,24,25</sup> and is lower than that of any other test (such as MRI, noncontrast CT, or needle aspiration).<sup>12</sup> The FP rate for PET imaging of adrenal lesions ranges from 0 to 8%.<sup>5,24,25</sup> PET imaging of the liver and lung has also been reported to have very low FN and FP rates,<sup>5</sup> making this an excellent study to either rule out or rule in malignant involvement in these sites (provided the lesion is  $\geq 1$  cm in diameter). However, because tissue confirmation of cancer is generally necessary, it may be more expeditious to perform a needle biopsy of a suspected metastatic site instead of a PET scan if the suspicion of malignant involvement is high.

### *cIII NSCLC*

A large proportion of patients with probable NSCLC present with radiographic evidence of mediastinal involvement but without signs and symptoms of systemic disease. In these patients, the FN rate of the clinical evaluation appears to be high enough (15 to 30%) to warrant a search for systemic metastases despite the negative clinical evaluation.<sup>12</sup> A PET scan is an alternative to the traditional approach using a bone scan, but it will not obviate the need for a brain CT or MRI. Although a PET scan may cost slightly more than a bone scan, a bone scan often results in indeterminate findings that prompt other imaging studies. Furthermore, PET imaging also has the advantage of potentially detecting unsuspected metastases at other sites. Thus, a rational argument can be made to consider a PET scan for extrathoracic staging in patients with cIII NSCLC.

Many studies<sup>3-5,23,26-28</sup> have reported finding dis-

tant metastases with PET in 10 to 40% of patients in general with lung cancer (often with limited verification of the PET results). Only one study<sup>29</sup> has characterized the patients carefully with regard to clinical evaluation and clinical stage. In this prospective study,<sup>29</sup> PET detected asymptomatic distant (nonbrain) metastases in 24% of 100 patients with cIII NSCLC. This rate of finding distant metastases in patients with cIII NSCLC is similar to the FN rate of the clinical evaluation in this patient population. In > 90% of these cases, the metastases were confirmed by cytology or follow-up, and no FP PET findings were noted. Of note, only 19% of the metastases involved the bone, suggesting an advantage for PET imaging over bone scan to look for asymptomatic distant disease. Similar results have been reported in two other studies<sup>30,31</sup> with respect to the clinical stage as defined by CT (but without data regarding the clinical evaluation): extrathoracic metastases were detected in 25% and 28% of patients with cIIIA,B NSCLC, respectively.<sup>30,31</sup>

It does not appear that PET imaging should replace mediastinoscopy for confirmation of the status of the mediastinum in centers where mediastinoscopy is available. Pooling the results from a large number of series suggests that the average FP rate of PET imaging in the mediastinum is 16%,<sup>10</sup> and a recent meta-analysis<sup>32</sup> found a FP rate of 22%. In another review<sup>33</sup> of data solely from patients with enlarged mediastinal nodes, the FP rate of PET in the mediastinum was an average of 13%. A positive PET scan result therefore warrants confirmation by mediastinoscopy at this time, and this was the conclusion reached in a recent evidence-based guideline as well.<sup>34</sup> Alternative approaches for confirmation of enlarged and suspicious nodes include transbronchial needle aspiration, TTNA, and esophageal ultrasound with needle aspiration.

Whether a negative PET scan finding in the mediastinum obviates the need for mediastinoscopy is a matter of controversy. Several reviews<sup>6,10,35,36</sup> have found average FN rates for PET in the mediastinum of 5 to 7% in general (involving patients with cIII as well as clinical stage I,II [cI,II] tumors). In a review<sup>33</sup> of data from patients with enlarged mediastinal nodes, the FN rate of PET in the mediastinum was an average of 8%. By comparison, the average FN rate for mediastinoscopy is 9% (range, 0 to 16%).<sup>10</sup> Although these are quite similar, some experts argue that it is important to find those patients with microscopic disease in the mediastinal lymph nodes, and that PET imaging will not detect this as well as mediastinoscopy.<sup>34,35</sup> Whether these results are interpreted as acceptable to avoid invasive biopsy in patients with a negative PET result, or as an argument to pursue this, is a matter of individual

opinion. However, it is likely that in patients with enlarged mediastinal nodes, many clinicians would be uncomfortable accepting a negative PET result without a biopsy. This is confirmed by a recent meta-analysis,<sup>37</sup> which estimated a 30% probability of malignant involvement of enlarged mediastinal nodes in the face of a negative PET scan.

In summary, PET imaging appears to be useful as an alternative to conventional imaging to rule out unsuspected systemic disease in patients with cIII NSCLC. Of course, information about the level of PET activity in the mediastinum will be gained as well. However, positive PET uptake in the mediastinum still warrants confirmation by mediastinoscopy (or other means). Although there is controversy about whether to accept a negative mediastinal PET scan in general, most clinicians would pursue mediastinoscopy in patients with enlarged mediastinal nodes by CT despite a negative PET result. However, in communities in which invasive staging of mediastinal nodes is not available, a strong argument for PET staging of the mediastinum can be made.

#### *cI,II NSCLC*

A search for distant metastases is traditionally thought to be unwarranted in patients with cI,II NSCLC if the clinical evaluation is negative, as several avenues of investigation consistently have found that the incidence of detectable metastases is < 5%.<sup>12</sup> It could be argued that these data are a reflection of the ability to detect metastases, and that PET imaging may have an increased detection rate. Two studies<sup>30,38</sup> have reported that PET detected extrathoracic metastases (subsequently confirmed) in 1% and 9% of patients who had cI,II tumors by radiographic assessment alone, without providing data about the clinical evaluation. PET detected distant metastases in 5.2% of 287 patients (77% clinical stage I [cI], 7% clinical stage II [cII], 16% cIIIA) with a negative clinical evaluation in another prospective trial (all metastases subsequently confirmed).<sup>39</sup> Only one study<sup>29</sup> has addressed the rate of detection of distant metastases specifically in patients with cI,II NSCLC by CT and by clinical evaluation. In this prospective study,<sup>29</sup> PET imaging detected asymptomatic distant (nonbrain) metastases in 8% of 39 patients with cI tumors and 18% of 28 patients with cII tumors.<sup>29</sup> This suggests that PET may be warranted for the detection of distant metastases in patients with cII tumors, whereas the detection rate in patients with cI tumors is probably not high enough to justify this test when all of the data are considered together. Of note, studies<sup>17,40</sup> evaluating the rate of detection of distant metastases by traditional tests after a negative clinical evaluation

have reported results for both cI and cII combined, although they have involved mostly cI disease.

Patients with cI,II tumors have a radiographically negative mediastinum by definition. However, there is ample evidence that the FN rate of CT for mediastinal involvement is approximately 20 to 25% in patients with central tumors, with an adenocarcinoma or with N1 node enlargement.<sup>10</sup> The rate of detection of mediastinal node involvement by PET imaging for such subsets of patients has never been reported. Thus, it is unclear whether PET can or should replace mediastinoscopy for mediastinal staging in patients with central tumors, adenocarcinoma, or clinical N1 disease.

If a PET scan has been obtained, the data suggest that a positive PET result in the mediastinum should be confirmed by a biopsy. In a review,<sup>33</sup> the FP rate of PET in the mediastinum for patients without mediastinal node enlargement was 14%, and other reviews<sup>10,31</sup> have found FP rates of 16% and 22% for patients in general, without regard to whether the nodes were enlarged or not. However, it is controversial whether or not to confirm a negative PET result in the mediastinum. The FN rate of PET in the mediastinum is 8% in patients with cI,II tumors,<sup>33</sup> and several reviews<sup>6,10,32,36</sup> have found average FN rates for PET in the mediastinum of 5 to 7% in general. Some physicians would argue that this FN rate is low enough to be acceptable, while others would argue that one should not rely on a negative PET study in clinical settings in which the chance of nodal involvement by CT criteria is high (central tumors, adenocarcinoma, or N1 node enlargement) because FN rates for PET have not been reported for such subsets of patients without mediastinal node enlargement.<sup>32,34</sup> A recent meta-analysis<sup>37</sup> estimated approximately a 5% probability of malignant involvement of normal-sized mediastinal nodes in the face of a negative PET scan, despite a pretest probability of malignant involvement of 25%.

In patients with peripheral cI tumors and a negative clinical evaluation, there appears to be little role for PET imaging for staging. The incidence of either systemic metastases or mediastinal node metastases in this population is quite low (< 10%).<sup>10,12</sup> Therefore, neither additional scans for distant disease nor mediastinoscopy are considered warranted in the traditional workup of these patients. The chance of detection of distant metastasis by PET is < 10% in patients with cI NSCLC,<sup>29,30,38</sup> making it difficult to justify PET imaging in these patients when one considers the problems of FP and equivocal results, and the resultant further testing and delays. With regard to the detection of possible mediastinal node involvement in patients with peripheral cI tumors, the fact that thoracotomy and node dissection dis-

closes < 10% with positive mediastinal nodes argues strongly against the use of PET for further mediastinal staging in these patients as well. A 10% rate of positive FDG uptake in the mediastinum among 84 patients with cI tumors was reported in the only study<sup>38</sup> that specifically addressed this population. However, 60% of these positive PET results in the mediastinum turned out to be FPs,<sup>38</sup> underscoring the drawbacks of pursuing such imaging if the incidence of disease is low. A lack of benefit to PET imaging is confirmed by a randomized study<sup>41</sup> consisting primarily (92%) of patients with cI NSCLC, in which there was no difference in the resection rate or incidence of early recurrences among 179 patients (mean follow-up, 10 months).

### CONCLUSION: WHO NEEDS A PET?

In patients who are estimated to have a high likelihood (> 80%) of having lung cancer, it is important to assess whether there are signs and symptoms of systemic metastases, whether there are radiographic signs of possible mediastinal nodal metastases, and whether the tumor is judged more likely to be SCLC or NSCLC. Any patient who has a moderate or higher chance of having systemic metastases should undergo imaging tests to confirm such metastases. This would include anyone with probable SCLC, anyone with a positive clinical evaluation suggesting systemic metastases (cIV), and any patient with radiographic evidence of mediastinal lymph node enlargement even in the face of a negative clinical evaluation (cIII). A reasonable approach in such patients with probable NSCLC would be to obtain a head CT (or MRI) and a PET scan (Table 2). An exception to this approach may be those patients with fairly obvious metastases in whom this can be confirmed by a biopsy of a metastatic site or by a skeletal plain radiograph

alone. An argument can also be made to pursue PET imaging to detect distant metastases in patients with a cII tumor, but the data are limited. The use of PET in patients with probable SCLC needs further study.

The role of PET imaging in intrathoracic staging is less clear. Staging of the mediastinum by PET is definitely better than staging by CT alone. Therefore, PET imaging has a definite role in mediastinal staging in communities or institutions where mediastinoscopy is not readily available. However, the reliability of PET imaging in the mediastinum in many instances is either not quite good enough or is not defined well enough to replace invasive biopsy as the ideal. Several prominent groups are moving away from reliance on PET results in favor of invasive biopsy with increasing experience with PET imaging.<sup>39,42,43</sup>

In patients with discrete mediastinal node enlargement by CT, mediastinoscopy (or other invasive biopsy) is likely to be indicated regardless of the PET findings in the mediastinum. A positive mediastinal PET result should be confirmed by a biopsy because the FP rate is approximately 15 to 20%. An exception to this policy can be justified in patients with a positive PET scan result and diffuse mediastinal infiltration by CT—in whom the CT appearance alone is generally accepted as reliable. A negative PET scan result, however, is also likely to prompt mediastinoscopy in patients with enlarged mediastinal nodes, especially when tissue confirmation of the diagnosis is still necessary.

In patients with no clinical evidence of systemic metastases and no evidence of mediastinal node involvement by CT, the role of PET imaging of the mediastinum is controversial. For certain subgroups of these patients (those with a central tumor, an adenocarcinoma, or N1 nodal involvement), the reliability of the negative CT result is notoriously poor (FN rate of 20 to 25%). The role of PET imaging of

**Table 2—Role of PET Imaging in Patients With Suspected Lung Cancer**

Clinical Scenario	Confirmation of Extrathoracic Stage	Confirmation of Intrathoracic Stage	Confirmation of Diagnosis
SCLC	Multiple scans vs PET*	Not applicable	Easiest site†
NSCLC			
cIV, multiple typical metastases	PET vs multiple scans*	Not applicable	Easiest site†
cIV, solitary potential metastasis	PET vs biopsy of suspected site	Not applicable	Easiest site† vs biopsy of suspected site
cIII, diffuse mediastinal infiltration	PET vs multiple scans	Radiographic	Easiest site†
cIII, discrete node enlargement	PET vs multiple scans	Mediastinal node biopsy	Mediastinal node biopsy
cII	PET vs clinical	Mediastinoscopy vs PET	Surgical resection
cI, peripheral	Clinical	Intraoperative node biopsy	Surgical resection

\*Unless the symptoms are highly suggestive and a simple radiographic test (eg, plain bone radiographs) are compelling.

†eg, sputum, bronchoscopy, fine-needle aspiration of supraclavicular node, TTNA.

the mediastinum has not been defined specifically for these subsets of patients, and mediastinoscopy remains the most reliable approach. A positive PET result would warrant confirmation by mediastinoscopy. Whether a negative PET result obviates the need for mediastinoscopy is controversial, with some physicians arguing that it should and others that it should not, and no data to resolve this.

In patients with a peripheral cI lung cancer, there are reasonable data to justify not pursuing a PET scan for staging. The evidence indicates that the incidence of finding either unsuspected distant metastases or unsuspected mediastinal involvement on PET imaging is quite low.

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**Seeking a Home for a PET, Part 2: Defining the Appropriate Place for Positron Emission Tomography Imaging in the Staging of Patients With Suspected Lung Cancer**

Frank C. Detterbeck, Steven Falen, M. Patricia Rivera, Jan S. Halle and Mark A. Socinski

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