Noninvasive Staging of Non-small Cell Lung Cancer*

ACCP Evidenced-Based Clinical Practice Guidelines (2nd Edition)

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Background: **Correctly staging lung cancer is important because the treatment options and the prognosis differ significantly by stage. Several noninvasive imaging studies including chest CT scanning and positron emission tomography (PET) scanning are available. Understanding the test characteristics of these noninvasive staging studies is critical to decision making.**

Methods: **Test characteristics for the noninvasive staging studies were updated from the first iteration of the lung cancer guidelines using systematic searches of the MEDLINE, HealthStar, and Cochrane Library databases up to May 2006, including selected metaanalyses, practice guidelines, and reviews. Study designs and results are summarized in evidence tables.**

Results: **The pooled sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were 51% (95% confidence interval [CI], 47 to 54%) and 85% (95% CI, 84 to 88%), respectively, confirming that CT scanning has limited ability either to rule in or exclude mediastinal metastasis. For PET scanning, the pooled estimates of sensitivity and specificity for identifying mediastinal metastasis were 74% (95% CI, 69 to 79%) and 85% (95% CI, 82 to 88%), respectively. These findings demonstrate that PET scanning is more accurate than CT scanning. If the clinical evaluation in search of metastatic disease is negative, the likelihood of finding metastasis is low.**

Conclusions: **CT scanning of the chest is useful in providing anatomic detail, but the accuracy of chest CT scanning in differentiating benign from malignant lymph nodes in the mediastinum is poor. PET scanning has much better sensitivity and specificity than chest CT scanning for staging lung cancer in the mediastinum, and distant metastatic disease can be detected by PET scanning. With either test, abnormal findings must be confirmed by tissue biopsy to ensure accurate staging.** ***(CHEST 2007; 132:178S–201S)***

Key words: CT scan; lung cancer; mediastinum; metastases; noninvasive; positron emission tomography; staging

Abbreviations: CI = confidence interval; FDG = fluoro-2-deoxy-D-glucose; NPV = negative predictive value; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PPV = positive predictive value; ROC = receiver operating characteristic; SCLC = small cell lung cancer

After a tissue diagnosis of lung cancer has been established or in patients in whom the clinical suspicion is high and surgery is the recommended next step, consideration must turn toward the determination of the extent of disease, or stage, because this will impact directly on management and prognosis. The most significant dividing line is between those patients who are candidates for surgical resection and those who are inoperable but will benefit from chemotherapy, radiation therapy, or both. Staging with regard to a patient's potential for surgical resection is most applicable to non-small cell lung cancer (NSCLC); whereas, for small cell lung cancer (SCLC) a more simplified staging classification of limited and extensive disease is employed. Except in rare cases of

surgically operable limited stage small cell cancer, the implication of staging on the management of SCLC is between chemotherapy and radiation for limited disease vs chemotherapy alone for extensive disease.[1]

The basis for staging NSCLC is the TNM system[2,3] (see Table 1 for TNM descriptors and Figure 1 for stage grouping). From a practical standpoint, the involvement of disease in the mediastinum, reflected in the N designator in the system, most often determines appropriateness for surgical resection.

Patients with sage IA, IB, IIA, and IIB disease can benefit from surgical resection. Patients with stage IIIA, IIIB, and IV disease almost never meet the criteria for surgery. The current role of chemotherapy followed by surgery for selected patients with stage IIIA disease remains controversial.

Staging can be used to predict survival and to guide the patient toward the most appropriate treatment regimen or clinical trial. Even with clinical stage I, surgically resectable, potentially curable disease, the 5-year survival rate after surgery is only 50%. Approximately 60% of cancer recurrences are presumably from extrathoracic micrometastatic involvement at presentation, which is not currently detectable with existing diagnostic modalities. Patients with clinical stage II disease (T1N1M0 or T2N1M0) have a 5-year survival rate after surgery of 30%. At clinical stage IIIA, the 5-year survival rate is 17%, and at stage IIIB it is only 5%.[3] These patients are generally treated with combined chemotherapy and radiotherapy. The 5-year survival rate for patients with stage IV disease is virtually nil, and this disease is treated either with chemotherapy and supportive care or with supportive care alone. Thus, one can see that it is critical to stage patients accurately as the treatment modalities and subsequent patient outcomes vary widely based on stage designation.

For this edition of the lung cancer guidelines, investigators from the Duke University Evidence-Based Practice Center and the authors of this guideline updated a systematic review of the diagnostic accuracy of noninvasive tests for staging in patients

Table 1—*TNM Descriptors*

Tumors	Description
Primary tumor (T)	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor < 3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)
T2	Tumor with any of the following features of size or extent: > 3 cm in greatest dimension; involves main bronchus; > 2 cm distal to the carina; invades the visceral pleura; and is associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3	Tumor of any size that directly invades any of the following chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium, or tumor in the main bronchus < 2 cm distal to the carina but without involvement of the carina or associated atelectasis or obstructive pneumonitis of the entire lung
T4	Tumor of any size that invades any of the following: mediastinum; heart; great vessels; trachea; esophagus; vertebral body; and carina or tumor with a malignant pleural or pericardial effusion or with satellite tumor nodule(s) within the primary tumor lobe of the lung
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumor
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis to contralateral mediastinal, contralateral, hilar ipsilateral or contralateral scalene or supraclavicular lymph node(s)
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

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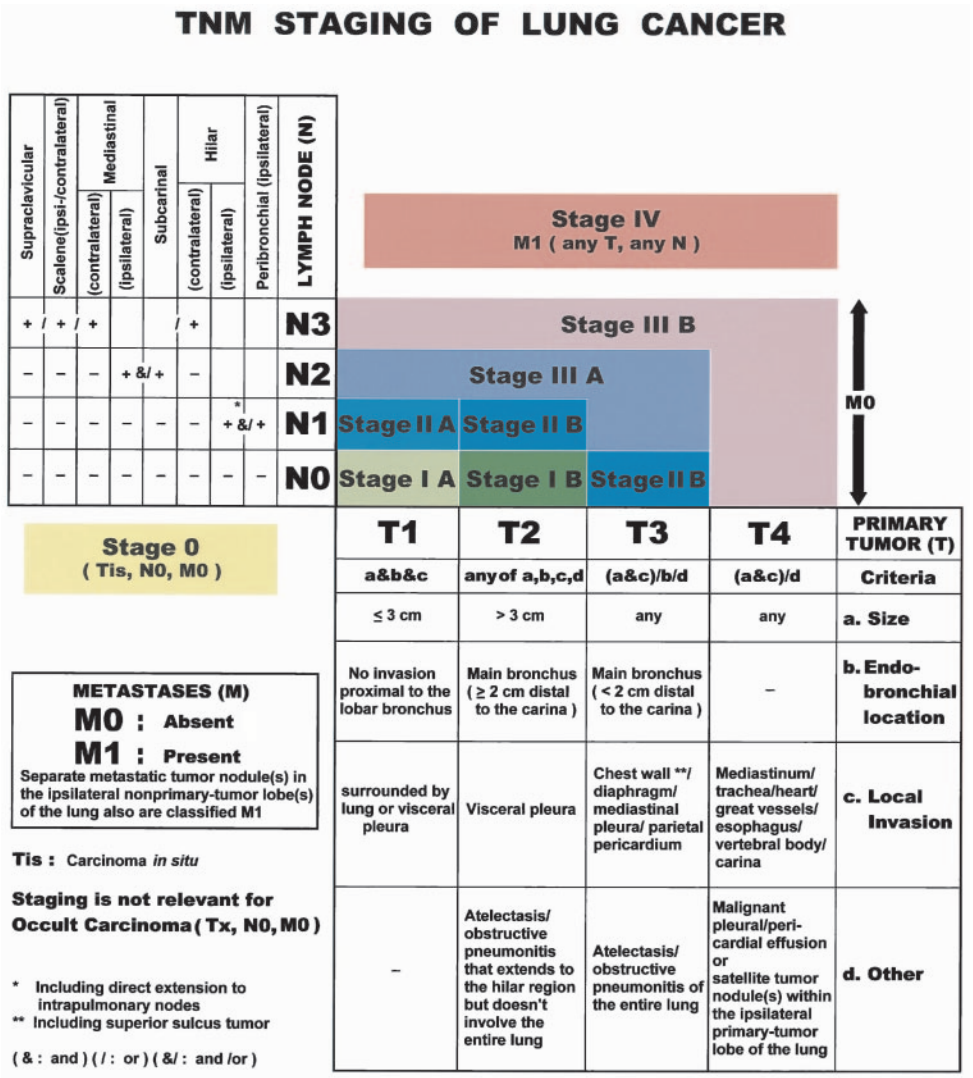

FIGURE 1. TNM staging of lung cancer.

with NSCLC. The methods and results of the initial review have been published previously and a more complete description of the methodology can be found there.[4] Briefly, the search strategy used computerized searches of the MEDLINE bibliographic database (January 1991 to May 2006), HealthStar, and the Cochrane Library. In addition, we searched the reference lists of included studies, selected textbooks, practice guidelines, systematic reviews, and metaanalyses in order to ensure that all relevant studies were identified. Only articles that had been published in English were considered.

SELECTION CRITERIA

Titles and abstracts, and the full text of all articles passing the title-and-abstract screen were evaluated independently by at least two of the authors for inclusion or exclusion based on the following five criteria: (1) publication in a peer-reviewed journal; (2) study size of 20 patients (except for studies involving CT scan evaluation of the mediastinum, for which 50 patients were required); (3) patient group not included in a subsequent update of the study; (4) histologic or cytologic confirmation of mediastinal nodes or extrathoracic sites in addition to the primary tumor; and (5) availability of the raw data needed to calculate independently the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of CT scanning, positron emission (PET) scanning, MRI, or endoscopic ultrasonography, or the raw data needed to calculate the NPV of the clinical evaluation.[4]

Grading Recommendations

Recommendations were developed by the writing committee, graded by a standardized method (see the "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and reviewed by all members of the lung cancer panel prior to approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

Noninvasive Staging of the Mediastinum

Staging is a critical part of the evaluation of every patient with lung cancer. Defining malignant involvement of the mediastinal lymph nodes is particularly important, as the status of these nodes will in many cases determine whether there is surgically resectable disease. the clinical staging of lung cancer is usually directed by noninvasive imaging modalities. On the basis of such tests, clinicians will determine the likelihood of the presence or absence of tumor involvement in regional lymph nodes.

In general, patients with lung cancer can be separated into four groups with respect to intrathoracic radiographic characteristics (including both the primary tumor and the mediastinum), as shown in Figure 2. Distinguishing these groups is particularly useful in defining the need for and selection of invasive staging tests. The first group (radiographic group A) involves patients with mediastinal infiltration that encircles the vessels and airways, so that discrete lymph nodes can no longer be discerned or measured. In these situations, the presence of mediastinal involvement (stage III disease) is generally accepted based on imaging studies alone, and the major issue is to obtain tissue by whatever approach is easiest in order to distinguish between SCLC and NSCLC. The second group (radiographic group B) involves patients with mediastinal node enlargement in whom the size of discrete nodes can be measured. In these patients, mediastinal nodal involvement is suspected but must be confirmed. The last two groups involve patients with normal mediastinal nodes. In radiographic group C, the presence of a central tumor or suspected N1 disease makes the chance of N2,3 nodal involvement relatively high (20 to 25%) despite normal-sized nodes, and further confirmation is needed.[5–8] In the final group (*ie*, those patients with a peripheral clinical stage I tumor), the chance of mediastinal involvement is quite low, and generally further confirmation of this is not needed (radiographic group D).[6–8]

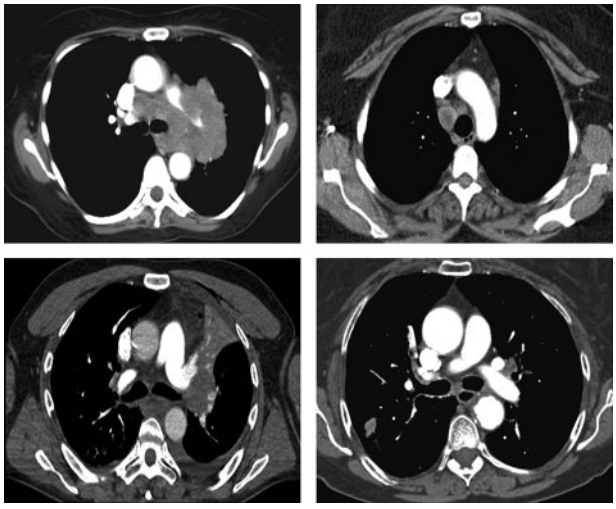

Figure 2. *Top left*: mediastinal infiltration by tumor. *Top right*: enlarged discrete N2,3 nodes. *Bottom left*: a central tumor or a tumor with enlarged N1 nodes, but a normal mediastinum. *Bottom right*: a peripheral small tumor (seen in lower left corner of image) with normal-sized lymph nodes.

A widely accepted definition of normal-sized mediastinal lymph nodes is a short-axis diameter of ≤ 1 cm on a transverse CT scan image. The term *discrete nodal enlargement* implies that discrete nodes are seen on the CT scan and are defined well enough to be able to measure their size (and are > 1 cm in size). Mediastinal infiltration is present when there is abnormal tissue in the mediastinum that does not have the appearance and shape of distinct lymph nodes, but instead has an irregular, amorphous shape. In this case, it is difficult to distinguish discrete nodes and impossible to come up with a measurement of the size of nodes. This occurs when multiple nodes are matted together to the point where the boundary between them is obscured, and can be assumed to involve extensive extranodal spread of the tumor. It may progress to the point where mediastinal vessels and other structures are partially or completely encircled. Finally, the distinction between a central tumor vs a peripheral tumor has also not been codified, but most authors consider any tumor in the outer two thirds of the hemithorax to be peripheral. Assessing the radiographic characteristics of the mediastinum will generally require that the clinician look at the images. This is because there is no standard format for how radiographic findings are reported (*eg*, the term *lymphadenopathy* is often used when there is a suspected malignancy, even though the mediastinal nodes are well below 1 cm in size).

The four radiographic groups are defined by anatomic characteristics seen on a CT scan (*ie*, size, location, and extent), and not by metabolic characteristics (*ie*, by PET scan) for many reasons. First, a CT scan is relatively inexpensive and essentially is

always performed as a preliminary step in order to define the nature of a pulmonary abnormality and to arrive at a clinical diagnosis of suspected lung cancer. Second, the information gained from the clinical history, physical examination, and chest CT can define whether other tests such as a PET scan are indicated. Finally, the technical considerations and performance characteristics of invasive staging procedures are likely to be driven primarily by anatomic characteristics rather than by metabolic ones. In other words, the location and size of a lymph node are important in determining how feasible and reliable an invasive test is, and these issues are unaffected by whether the node in question is metabolically active on PET scanning or not. Further discussion of the best approach to confirming a diagnosis of mediastinal tumor involvement by tissue acquisition can be found in chapter 13 of this supplement on invasive staging.

Chest Radiograph

The majority of lung cancers are initially detected on a plain chest radiograph. In some situations, the plain radiograph may be sufficient to detect spread of the tumor to the mediastinum. For example, the presence of bulky lymphadenopathy in the superior or contralateral mediastinal areas may be considered adequate evidence of metastatic disease, precluding a further imaging evaluation of the chest. This may be particularly true if the patient is too ill or is unwilling to undergo treatment of any kind. However, it is recommended that tissue confirmation be obtained if possible by the least invasive method available. It is widely accepted that the chest radiograph is in general an insensitive measure of mediastinal lymph node involvement with lung cancer; thus, further noninvasive and/or invasive assessment is usually necessary.

CT Scan of the Chest

CT scanning of the chest is the most widely available and commonly used noninvasive modality for evaluation of the mediastinum in lung cancer. The vast majority of reports evaluating accuracy of CT scanning for mediastinal lymph node staging have employed the administration of IV contrast material. IV contrast is not absolutely necessary in performing chest CT scanning for this indication, but may be useful in helping to distinguish vascular structures from lymph nodes as well as in delineating mediastinal invasion by centrally located tumors. A CT scan of the chest should be performed in all cases of lung cancer unless the patient is so debilitated that no treatment is planned or they are unwilling to undergo further evaluation.

Various CT scan criteria have been used to define the malignant involvement of mediastinal lymph nodes. Notwithstanding the radiographic descriptions of mediastinal nodal involvement, the most widely used criterion is a short-axis lymph node diameter of ≥ 1 cm on a transverse CT scan. However, numerous other criteria have also been used including the following: (1) a long-axis diameter of ≥ 1 cm; (2) a short-axis diameter of ≥ 1.5 cm; (3) a short-axis diameter ≥ 1 cm plus evidence of central necrosis or disruption of the capsule; and (4) a short-axis diameter of ≥ 2 cm regardless of nodal morphology. The reported sensitivity and specificity for identifying malignant involvement will vary depending on which criteria are used in the assessment of individual nodal stations.[9,10] The majority of studies evaluating CT scan accuracy have used a short-axis diameter of ≥ 1 cm as the threshold for abnormal nodes. In doing so, a conscious effort has been made to strike an appropriate balance between sensitivity and specificity in an understandable effort to minimize the number of false-positive evaluations without producing an unacceptable number of false-negative evaluations.

For the purposes of these guidelines, investigators from the Duke University Evidence-based Practice Center and the authors of this section of the supplement conducted a systematic review of the medical literature relating to the accuracy of CT scanning for noninvasive staging of the mediastinum in patients with lung cancer.[4] Thirty-five studies published from 1991 through June 2006 evaluating the performance characteristics of CT scanning for this purpose were identified based on their fulfillment of the following criteria: (1) publication in a peer-reviewed journal; (2) a study size of > 50 patients; (3) patient group not included in a subsequent update of the study; (4) histologic or cytologic confirmation of mediastinal nodes or extrathoracic site as well as the primary tumor; and (5) availability of the raw data needed to calculate independently sensitivity, specificity, PPV, and NPV. These 43 studies[6,11–44,52,87,121,122,178–181] are outlined in Table 2. The combined studies yielded 5,111 evaluable patients.[6,11–44,52,87,121,122,178–181] The median prevalence of mediastinal metastasis was 28% (range, 18 to 56%). Almost all studies specified that CT scanning was performed following the administration of IV contrast material and that a positive test result was defined as the presence of one or more lymph nodes that measured > 1 cm on the short-axis diameter. Individual study estimates of sensitivity and specificity are shown in Figure 3, which also displays the summary receiver operator characteristic (ROC) curve for mediastinal staging

Table 2—*Accuracy of CT Scanning for Staging the Mediastinum in Lung Cancer Patients**

Study/Year	Patients, No.	CT Scan Technique	Sensitivity	Specificity	PPV	NPV	Prevalence
Analysis by nodal station							
Gupta et al[52]/2000	54	Contrast	0.68	0.31	0.31	0.68	0.32
Berlangieri et al[178]/1999	50	Contrast	0.65	0.9	0.41	0.96	0.1
Graeber et al[121]/1999	96	Contrast	0.63	0.6	0.51	0.71	0.4
Gupta et al[122]/1999	103	Contrast	0.64	0.61	0.52	0.72	0.4
Kernstine et al[87]/1999	64	Contrast	0.65	0.79	0.37	0.92	0.16
Vansteenkiste et al[24]/1998	68	Contrast	0.96	0.45	0.96	0.47	0.93
Vansteenkiste et al[25]/1998	56	Contrast	0.95	0.64	0.95	0.63	0.88
Kobayashi and Kitamura[179]/1995	76	Contrast	0.76	0.76	0.78		
Primack et al[18]/1994	159	Contrast	0.58	0.86	0.71	0.77	0.38
Seely et al[180]/1993	104	Contrast	0.48	0.94	0.4	0.96	0.07
Izbicki et al[181]/1992	108	Contrast	0.24	0.93	0.44	0.84	0.18
Summary	938		0.86	0.79	0.82	0.84	0.52
Analysis by patient							
Takamochi et al[12]/2005	71	Contrast	0.20	0.89	0.33	0.81	0.21
Pozo-Rodriguez et al[6]/2005	132	Contrast	0.86	0.67	0.49	0.93	0.27
Nomori et al[11]/2004	80	NR	0.5	0.95	0.70	0.90	0.18
Kelly et al[44]/2004	69	Contrast	0.46	0.86	0.43	0.87	0.19
Kimura et al[43]/2003	203	Contrast	0.63	0.97	0.88	0.89	0.24
Reed et al[42]/2003	302	Contrast	0.37	0.91	0.58	0.81	0.25
Schillaci et al[41]/2003	83	Contrast	0.69	0.75	0.67	0.77	0.42
Eggeling et al[40]/2002	73	Contrast	0.82	0.50	0.79	0.55	0.70
Kiernan et al[39]/2002	92	Contrast	0.64	0.94	0.80	0.88	0.27
Nosotti et al[38]/2002	87	Contrast	0.64	0.88	0.64	0.88	0.25
von Haag et al[37]/2002	52	Contrast	0.50	0.65	0.16	0.91	0.12
Laudanski et al[36]/2001	92	Contrast	0.60	0.73	0.51	0.79	0.33
Poncelet et al[35]/2001	62	Contrast	0.56	0.68	0.23	0.90	0.15
Wallace et al[34]/2001	121	Contrast	0.87	0.35	0.75	0.54	0.69
Dunagan et al[33]/2001	72	Contrast	0.50	0.87	0.56	0.84	0.25
Kamiyoshihara et al[32]/2001	546	Contrast	0.33	0.90	0.46	0.84	0.20
Osada et al[31]/2001	335	Contrast	0.56	0.93	0.77	0.83	0.30
Pieterman et al[30]/2000	102	Contrast	0.75	0.66	0.50	0.85	0.31
Takamochi et al[29]/2000	401	Contrast	0.30	0.82	0.30	0.83	0.20
Marom et al[28]/1999	79	Contrast	0.59	0.86	0.84	0.63	0.56
Saunders et al[27]/1999	84	NR	0.20	0.90	0.30	0.84	0.18
Suzuki et al[26]/1999	440	Contrast	0.33	0.92	0.56	0.82	0.23
Vansteenkiste et al[25]/1998	68	Contrast	0.75	0.63	0.58	0.78	0.41
Vansteenkiste et al[24]/1998	56	Contrast	0.86	0.79	0.80	0.85	0.50
Bury et al[20]/1997	64	Contrast	0.79	0.84	0.58	0.93	0.22
Gdeedo et al[23]/1997	100	Contrast	0.63	0.57	0.41	0.76	0.32
Buccheri et al[21]/1996	80	Contrast	0.64	0.74	0.48	0.84	0.28
Bury et al[22]/1996	53	Contrast	0.71	0.81	0.63	0.85	0.32
Aaby et al[19]/1995	57	NR	0.72	0.91	0.86	0.81	0.44
Primack et al[18]/1994	159	Contrast	0.63	0.86	0.73	0.79	0.38
Yokoi et al[17]/1994	113	Contrast	0.62	0.80	0.61	0.81	0.33
McLoud et al[16]/1992	143	Contrast	0.64	0.62	0.44	0.79	0.31
Jolly et al[15]/1991	336	Contrast	0.71	0.86	0.69	0.87	0.30
Cole et al[14]/1993	150	NR	0.26	0.81	0.26	0.81	0.21
Webb et al[13]/1991	154	Contrast	0.52	0.69	0.31	0.84	0.21
Summary	5,111		0.51 (0.47–0.54)	0.86 (0.84–0.88)			0.28

*NR = not reported.

with CT scanning. ROC curves illustrate the tradeoff between sensitivity and specificity as the threshold that defines a positive test result varies from most to least stringent. The summary ROC method rests on the assumption that individual study estimates of sensitivity and specificity represent unique points on a common ROC curve. A summary ROC curve that lies closer to the upper left-hand corner of the diagram indicates better overall diagnostic accuracy. The pooled sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were 51% (95% confidence interval [CI], 47 to 54%) and 86% (95% CI, 84 to 88%), respectively. The corresponding positive and negative likelihood ratios were 3.4 and 0.6, respectively, confirming that CT scanning has a limited ability either to rule in or

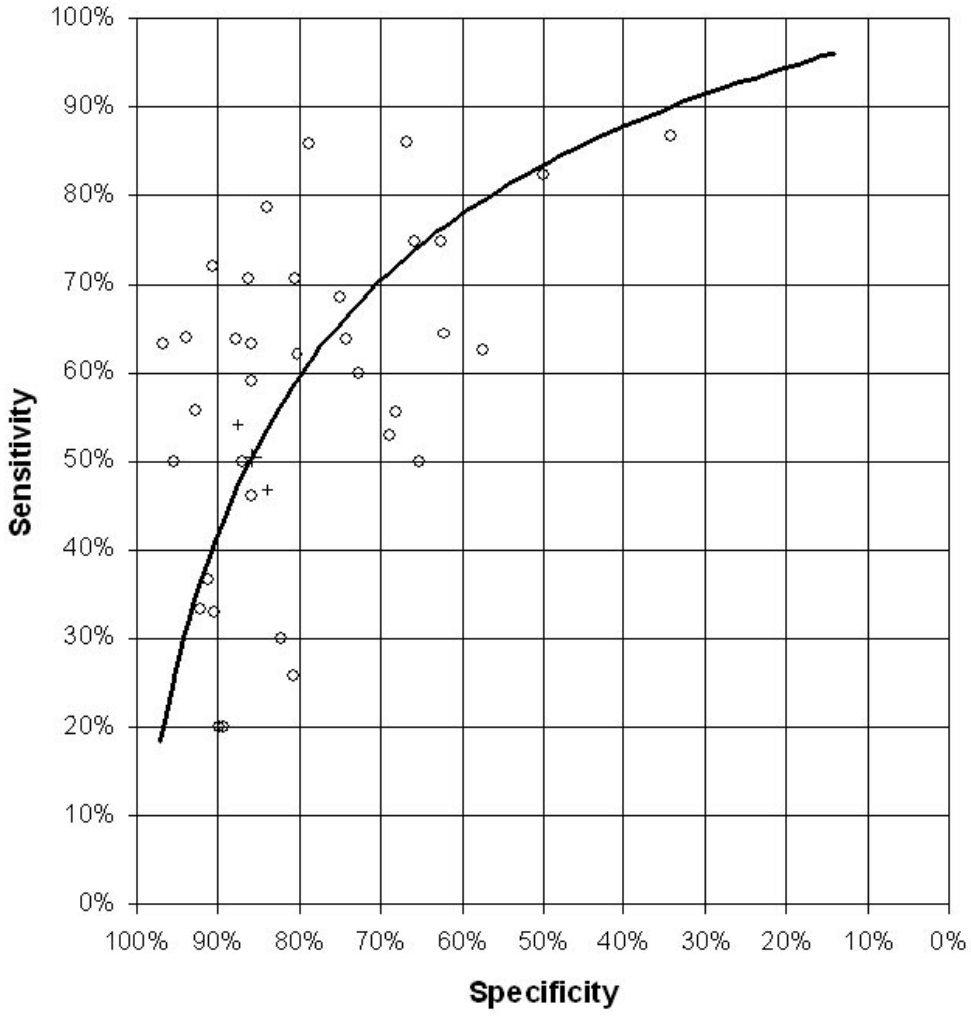

FIGURE 3. Summary ROC curve for imaging mediastinal lymph nodes > 1 cm in diameter with a standard CT scan. Open circles = individual study estimates of sensitivity and specificity (a study showing the highest accuracy will appear in the top left corner of the graph); dark line = summary ROC curve; large "+" = sensitivity and specificity at the mean threshold point on the summary ROC curve; smaller "+" = 95% CIs about the mean threshold summary sensitivity and specificity estimates.

exclude mediastinal metastasis. The combined estimates should be interpreted with caution as the studies were statistically heterogeneous. Still, these findings mirror those of other analyses addressing the accuracy of CT scanning for staging the mediastinum in NSCLC. A large metaanalysis by Gould and colleagues[45] reported the median sensitivity and specificity of CT scanning for identifying malignant mediastinal nodes as 61% and 79%, respectively, while an earlier metaanalysis by Dwamena and colleagues[46] reported average sensitivity and specificity of 64% and 74%, respectively.

CT scanning is clearly an imperfect means of staging the mediastinum, but it remains the best overall anatomic study available for the thorax. A CT scan usually guides the choice of nodes for selective node biopsy by invasive techniques, and thus continues to be an important tool for diagnosing lung cancer. The choice of individual nodes for sampling as well as the choice of the most appropriate invasive technique (including transbronchial, transthoracic, or transesophageal needle aspiration, mediastinoscopy, or more extensive surgery) will typically be directed by the findings of the CT scan. However, the limitation of CT scan-based mediastinal lymph node evaluation is evident in the fact that 5 to 15% of patients with clinical T1N0 (clinical stage I) tumors will be found to have positive lymph node involvement by surgical lymph node sampling.[47]

Based on the currently available data relating to the performance characteristics of CT scanning for the evaluation of the mediastinum in patients with NSCLC, two important messages emerge. First, approximately 40% of all nodes that are deemed to

be malignant by CT scan criteria are actually benign. Patient characteristics are a large factor, as specificity can be affected by clinical factors such as the presence of postobstructive pneumonitis.[16] Second, approximately 20% of all nodes that are deemed to be benign by CT scan criteria are actually malignant. CT scanning can thus both overstage and understage the mediastinal nodes. In sum, there is no node size that can reliably determine tumor stage and operability. In cases in which the CT scan criteria for the identification of a metastatic node are met, the clinician must still prove beyond a reasonable doubt by biopsy or resection that the node is indeed malignant. Given the limitations of its imperfect sensitivity and specificity, it is usually inappropriate to rely solely on the CT scan to determine mediastinal lymph node status in patients with NSCLC. Nonetheless, CT scanning continues to play an important and necessary role in the evaluation of these patients. This conclusion is supported by the most recent American Thoracic Society/European Respiratory Society statement[47] on the pretreatment evaluation of NSCLC and British Thoracic Society guidelines[48] on the selection of patients with lung cancer for surgery, both of which recommend CT scanning for the evaluation of mediastinal lymph nodes in all patients with suspected NSCLC. In the mediastinum, a CT scan can provide a road map that guides the location and modality to be used for subsequent biopsy procedures. In addition, patients with a very low pretest probability of metastasis (*eg*, those with small, peripheral T1 primary tumors) and no evidence of lymph node enlargement on a CT scan arguably might not require invasive staging prior to definitive thoracotomy. For example, when the clinical pretest probability is 10%, the posttest probability is approximately 6% when CT scan results are negative in the mediastinum.

Recommendations

1. For patients with either a known or suspected lung cancer who are eligible for treatment, a CT scan of the chest with contrast including the upper abdomen (liver and adrenal glands) should be performed. Grade of recommendation, 1B

2. In patients with enlarged discrete mediastinal lymph nodes on CT scans (> 1 cm on the short axis) and no evidence of metastatic disease, further evaluation of the mediastinum should be performed prior to definitive treatment of the primary tumor. Grade of recommendation, 1B

PET Scanning

PET scanning is an imaging modality based on the biological activity of neoplastic cells. Lung cancer cells demonstrate increased cellular uptake of glucose and a higher rate of glycolysis when compared to normal cells.[49] The radiolabeled glucose analog ^{18}F-fluoro-2-deoxy-D-glucose (FDG) undergoes the same cellular uptake as glucose and is phosphorylated by hexokinase, generating ^{18}F-FDG-6-phosphate. The combination of increased uptake of ^{18}F-FDG and a decreased rate of dephosphorylation by glucose-6-phosphatase in malignant cells results in an accumulation of ^{18}F-FDG-6-phosphate in these cells.[50,51] The concentrated isotope can then be identified using a PET camera. FDG-PET (subsequently referred to as PET) is thus a metabolic imaging technique that is based on the function of a tissue rather than its anatomy. Standardized quantitative criteria for an abnormal PET scan finding in the mediastinum are unfortunately lacking. A qualitative assessment is usually based on a comparison of uptake in the lesion or structure in question compared to the background activity of the lung or liver. A standard uptake value of < 2.5 is sometimes used as a threshold level for normalcy, but this measurement may vary with the new generation of scanners. Despite the lack of standardized criteria defining positive findings, PET scanning has proved useful in differentiating neoplastic from normal tissues. However, the technique is not infallible as nonneoplastic processes including granulomatous and other inflammatory diseases as well as infections may also demonstrate positive PET imaging findings. Further, size limitations are an issue, with the lower limit of spatial resolution of the current generation of PET scanners being approximately 7 to 10 mm. However, smaller lesions may be detected, depending on the intensity of uptake of the isotope in abnormal cells.[30,52] Additionally, certain well-differentiated low-grade malignancies, particularly bronchioloalveolar cell carcinoma and typical carcinoid tumors, are known to have higher false-negative finding rates.[53–57]

A burgeoning number of studies in the last several years have reported on the utility of PET scanning in the assessment of the mediastinum in patients with lung cancer. The increasing availability of the technology now allows PET scanning to be used widely as a diagnostic tool. It should be noted that PET scanning is primarily a metabolic examination and has limited anatomic resolution. It is usually possible by PET scanning to identify lymph node stations, but not individual lymph nodes. CT scanning provides much more anatomic detail but lacks the functional information provided by PET scanning. Newer generation inte-

grated PET-CT imagers may combine the advantages of both studies, but there are as yet few studies addressing the accuracy of this modality.[58]

As was done for CT scanning, investigators from the Duke University Evidence-based Practice Center performed a systematic review[4] of the medical literature relating to the accuracy of PET scanning for noninvasive staging of the mediastinum in patients with lung cancer. Studies evaluating the performance characteristics of PET scanning for this purpose were identified based on their fulfillment of the following criteria: (1) publication in a peer-reviewed journal; (2) study size of > 20 patients; (3) patient group not included in a subsequent update of the study; (4) histologic or cytologic confirmation of mediastinal nodes or extrathoracic site as well as the primary tumor; and (5) availability of the raw data needed to calculate independently sensitivity, specificity, PPV, and NPV. All studies were interpreted in conjunction with patients' CT scan findings so that the PET scan findings were correlated with the anatomic location of the lesion seen on the CT scan. In all studies, ^{18}F-FDG was the radiopharmaceutical used for imaging. Forty-four studies [6,8,11,12,20,22,24,25,27,28,30,33,35,37,39,42,44,52,59–78,87,121,122,178,182,183] published between 1994 and June 2006 were identified, yielding 2,865 evaluable patients. These studies are displayed in Table 3. The median prevalence of mediastinal metastasis was 29% (range, 5 to 64%). Figure 4 shows individual study estimates of sensitivity and specificity and the summary ROC curve for the PET scans. Pooled estimates of sensitivity and specificity for identifying mediastinal metastasis were 74% (95% CI, 69 to 79%) and 85% (95% CI, 82 to 88%), respectively. Corresponding positive and negative likelihood ratios for mediastinal staging with PET scanning were 4.9 and 0.3, respectively. These findings demonstrate that PET scanning is more accurate than CT scanning for staging of the mediastinum in patients with lung cancer, though it is far from perfect.

PET scanning may provide an additional benefit in that it is a whole-body study. The usual extrathoracic staging of lung cancer will typically include a combination of bone scintigraphy, brain imaging by CT scanning or MRI and abdominal CT scanning or the inclusion of the upper abdomen in a chest CT scan. PET scanning is able to provide information about the primary site in the chest as well as intrathoracic and extrathoracic metastases with a single study. The exception to this is the definition of metastases in the brain, as the brain will normally avidly take up ^{18}F-FDG. Several studies[30,42,79] have reported on the ability of PET scanning to identify extrathoracic metastases in patients whose tumors had been deemed resectable by conventional imaging. The rate of detection of unanticipated M1 disease by PET scanning has been reported as 1 to 8% in patients with clinical stage I disease and 7 to 18% in patients with clinical stage II disease.[42,79] The identification of unanticipated distant metastases by PET scanning in such patients should result in the avoidance of unwarranted thoracotomies, but all positive findings in surgical candidates should be confirmed by biopsy unless there is overwhelming evidence of distant metastasis.[80]

To summarize, PET scanning has both higher sensitivity and higher specificity than CT scanning for the evaluation of mediastinal lymph nodes, and can provide important information regarding the presence of metastatic disease outside the thorax. In the mediastinum, PET scanning is more accurate than CT scanning in identifying abnormal nodes that can be sampled by directed biopsy. Accordingly, PET scanning has assumed an increasingly important role in the evaluation of patients with lung cancer. However, broader experience with PET scanning has not yet allowed a precise definition of its role in the staging evaluation of lung cancer. PET scanning is not infallible. False-positive PET scan findings may result in missed opportunities for a cure by surgical resection. Conversely, false-negative PET scan findings may lead to fruitless thoracotomies in patients with unresectable disease. The potential consequences of both false-positive and false-negative PET scan findings in an environment in which PET scanning is increasingly relied on for staging must be considered when PET scanning is included in the evaluation of NSCLC.

Some studies[45,81–83] have pointed out that the accuracy of PET imaging in the mediastinum is dependent on the size of the nodes identified by CT scanning. PET scanning is more sensitive (but less specific) when CT scanning identifies enlarged nodes.[45,81] In a metaanalysis evaluating the conditional test performance of PET and CT scanning, Gould and colleagues[45] reported median sensitivity and specificity of PET scans of 100% and 78%, respectively, in patients with enlarged lymph nodes. PET scanning is thus very accurate in identifying malignant nodal involvement when nodes are enlarged. However, PET scanning will falsely identify malignancy in approximately one-fourth of patients with nodes that are enlarged for other reasons, usually inflammation, or infection. Positive PET findings in this situation should be confirmed by directed biopsy. Failure to do so could result in patients with surgically resectable disease being denied curative surgery. An argument could also be made that a patient in whom the clinical assessment of pretest probability of malignant node involvement is high should proceed directly to biopsy without PET, as a negative

Table 3—*Accuracy of PET Scanning for Staging the Mediastinum in Lung Cancer Patients*

Study/Year	Patients, No.	Sensitivity	Specificity	PPV	NPV	Prevalence
Analysis by nodal station						
Gupta et al[52]/2000	54	0.96	0.93	0.86	0.98	0.32
Yasukawa et al[182]/2000	41	0.86	0.91	0.79	0.94	0.29
Berlangieri et al[178]/1999	50	0.8	0.97	0.73	0.98	0.1
Graeber et al[121]/1999	96	0.98	0.94	0.91		
Gupta et al[122]/1999	103	0.92	0.95	0.92	0.95	0.4
Kernstine et al[87]/1999	64	0.7	0.86	0.48	0.94	0.16
Vansteenkiste et al[24]/1998	68	0.99	0.86	0.99	0.89	0.93
Vansteenkiste et al[25]/1998	56	0.93	0.47	0.92	0.5	0.87
Steinert et al[63]/1997	47	0.89	0.99	0.96	0.97	0.25
Sasaki et al[183]/1996	29	0.76	0.98	0.93	0.93	0.24
Summary	608	0.95	0.9	0.94	0.92	0.61
Analysis by patient						
Takamochi et al[12]/2005	71	0.40	0.88	0.46	0.84	0.21
Pozo-Rodriguez et al[6]/2005	132	0.81	0.76	0.56	0.91	0.27
Halpern et al[78]/2005*	36	0.5	0.77	0.45	0.80	0.28
Verhagen et al[8]/2004	56	0.58	0.90	0.83	0.71	0.46
Nomori et al[11]/2004	80	0.86	0.97	0.86	0.97	0.18
Kelly et al[44]/2004	69	0.62	0.98	0.89	0.92	0.19
Demura et al[77]/2003	50	0.87	0.63	0.50	0.92	0.30
Fritscher-Ravens et al[76]/2003	33	0.75	0.88	0.86	0.79	0.48
Gonzalez-Stawinski et al[75]/2003	202	0.66	0.78	0.48	0.88	0.23
Konishi et al[74]/2003	54	0.80	0.92	0.50	0.98	0.09
Reed et al[42]/2003	302	0.61	0.84	0.56	0.87	0.25
Zimny et al[73]/2003	33	0.83	0.81	0.71	0.89	0.36
Kernstine et al[72]/2002	237	0.82	0.82	0.51	0.95	0.19
Kiernan et al[39]/2002	88	0.88	0.86	0.71	0.95	0.28
Vesselle et al[71]/2002	118	0.81	0.96	0.92	0.90	0.36
von Haag[37]/2002	52	0.67	0.91	0.50	0.95	0.12
Changlai et al[70]/2001	127	0.88	0.83	0.90	0.79	0.64
Poncelet et al[35]/2001	61	0.67	0.85	0.43	0.94	0.15
Tatsumi et al[69]/2000	21	0.80	0.82	0.80	0.82	0.48
Dunagan et al[33]/2001	81	0.52	0.88	0.61	0.84	0.26
Farrell et al[68]/2000	84	1.00	0.93	0.40	1.00	0.05
Liewald et al[67]/2000	76	0.93	0.78	0.69	0.95	0.35
Pieterman et al[30]/2000	102	0.91	0.86	0.74	0.95	0.31
Roberts et al[66]/2000	100	0.88	0.91	0.75	0.96	0.24
Magnani et al[65]/1999	28	0.67	0.84	0.67	0.84	0.32
Marom et al[28]/1999	79	0.73	0.94	0.85	0.88	0.56
Saunders et al[27]/1999	84	0.71	0.97	0.86	0.93	0.20
Vansteenkiste et al[24]/1998	68	0.93	0.95	0.93	0.95	0.41
Vansteenkiste et al[25]/1998	56	0.86	0.43	0.60	0.75	0.50
Bury et al[20]/1997	64	0.86	1.0	1.0	0.96	0.22
Guhlmann et al[64]/1997	32	0.87	1.0	1.0	0.89	0.47
Steinert et al[63]/1997	47	0.92	0.97	0.92	0.97	0.28
Bury et al[22]/1996	30	0.88	0.86	0.88	0.86	0.53
Sazon et al[62]/1996	32	1.00	1.00	1.00	1.00	0.50
Scott et al[61]/1996	27	1.00	1.00	1.00	1.00	0.33
Chin et al[60]/1995	30	0.78	0.81	0.64	0.89	0.30
Wahl et al[59]/1994	23	0.82	0.75	0.75	0.82	0.48
Summary	2,865	0.74 (0.69–0.79)	0.85 (0.82–0.88)			0.29

*Calculations are based on the data reported in Table 2. The results of this study should be interpreted with caution as there is a minor inconsistency between the results in the text and those in Table 3.

PET result would not negate a strong clinical suspicion for tumor. In this situation, negative PET findings would be unlikely to change the clinical suspicion for malignancy enough to defer histologic confirmation. As a counter-argument, PET scanning might still impact the decision process if unexpected extra-thoracic sites of abnormal activity are found, and patients with clinical stage III disease are at highest risk for occult distant metastasis. Identification of such foci might affect the choice of biopsy site and have a significant impact on the clinical stage and the

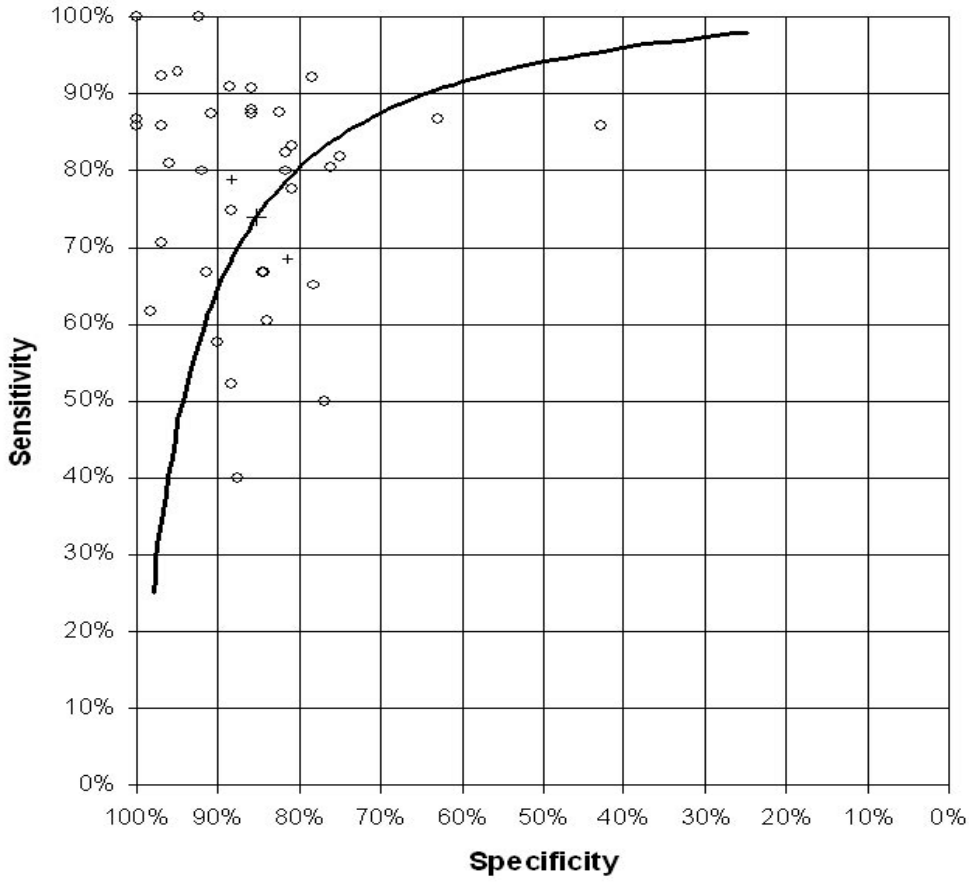

FIGURE 4. Summary ROC curve for imaging mediastinal lymph nodes > 1 cm diameter with FDG-PET scanning. Open circles = individual study estimates of sensitivity and specificity (a study showing the highest accuracy will appear in the top left corner of the graph); dark line = summary ROC curve; larger "+" = sensitivity and specificity at the mean threshold point on the summary ROC curve; smaller "+" = 95% CIs about the mean threshold summary sensitivity and specificity estimates.

decision of whether a patient should undergo surgical resection. Whether this is adequate reason to pursue PET scanning in patients with enlarged mediastinal nodes by CT scanning in whom the clinical suspicion for malignant involvement is high is unanswered.

Conversely, PET scanning is less sensitive (but more specific) in patients with normal-sized mediastinal nodes seen by CT scanning. Based on the data presented in Table 2, CT scanning of the mediastinum is falsely negative in approximately 20% of patients with normal-sized nodes and malignant nodal involvement. In the metaanalysis reported by Gould and colleagues,[45] the median sensitivity and specificity of PET scanning in this group of patients were 82% and 93%, respectively. These data indicate that nearly 20% of patients with normal-sized nodes but with malignant involvement had falsely negative PET scan findings. Corresponding positive and negative likelihood ratios were approximately 12.0 and 0.2, respectively. In this study, when both CT and PET scan results were negative and the pretest probability of mediastinal lymph node metastasis was estimated at 35% (which corresponds to the median prevalence of mediastinal metastasis in studies of PET scanning), the posttest probability of mediastinal metastasis was approximately 9% (95% CI, 4 to 14%). This addresses the controversial question of whether a negative PET scan finding in patients with normal-sized lymph nodes by CT scanning can obviate the need to perform further invasive mediastinal evaluation prior to thoracotomy. In this situation, we believe that the appropriate invasive staging procedure would be mediastinoscopy, as there are no enlarged nodes to directly biopsy by other techniques. While PET scanning samples all mediastinal nodal groups, it is clearly less sensitive for nodes with a diameter of < 7 to 10 mm. While mediastinoscopy cannot sample all mediastinal nodal groups, it can detect microscopic disease even in small nodes. Ultimately, the decision as

to whether a negative PET scan finding can be used to obviate mediastinoscopy will require clinical judgment that incorporates multiple factors, including the clinical pretest probability of mediastinal metastasis, patient preferences, and local availability and expertise in both mediastinoscopy and PET imaging (see the "Invasive Mediastinal Staging of Lung Cancer" chapter for further recommendations).

The utility of PET scanning in patients with stage 1A disease is less clear as the prevalence of mediastinal and distant metastatic disease is low and the evidence for utilizing PET scanning is poor. Further study in this specific patient population is warranted prior to making a recommendation that has a higher level of evidence.

In summary, PET scanning is the most accurate noninvasive imaging modality available to evaluate the mediastinum in patients with lung cancer. Abnormal findings on PET scans may be important in identifying mediastinal nodes for directed biopsy. PET scanning is also a whole-body study and offers additional information relating to extrathoracic sites of possible disease involvement (see "The Search for Metastatic Disease" section). However, wider experience with PET scanning has increased the awareness of the potential for and consequences of both false-positive and false-negative findings.

Recommendations

3. PET scanning to evaluate for mediastinal and extrathoracic staging should be considered in patients with clinical 1A lung cancer being treated with curative intent. Grade of recommendation, 2C

4. Patients with clinical 1B-IIIB lung cancer being treated with curative intent, should undergo PET scanning (where available) for mediastinal and extrathoracic staging. Grade of recommendation, 1B

5. In patients with an abnormal result on FDG-PET scans, further evaluation of the mediastinum with sampling of the abnormal lymph node should be performed prior to surgical resection of the primary tumor. Grade of recommendation, 1B

Integrated PET and CT Scanning

An important shortcoming of dedicated PET imaging is its limited spatial resolution, which results in poor definition of anatomic structures. As a result, it may be difficult for PET scanning to distinguish between mediastinal and hilar lymph nodes, or to differentiate between a central primary tumor and a lymph node metastasis, even when the results of PET and CT scans are visually correlated. This limitation has been addressed by the development of "dual-modality" or "integrated" PET/CT scanning systems, in which a CT scanner and a PET scanner are combined in a single gantry. Some studies[24,25,58,84,85] have begun to examine the accuracy of integrated PET/CT scanners for lung cancer staging. The total number of patients evaluated by this hybrid technique is still relatively small. Estimates of accuracy for identifying mediastinal metastasis are limited, though early studies have indicated[24,25,85] that the sensitivity and specificity are at least as good as those with PET scanning alone.

MRI for Staging the Mediastinum

Like CT scanning, MRI is an anatomic study. Data relating to the accuracy of the evaluation of the mediastinum with MRI in patients with NSCLC are limited, but available reports[13,86] suggest that the accuracy of MRI is as good as CT scanning. Two reports[86,87] also have suggested that the use of contrast enhancement may improve the accuracy of MRI in this situation. MRI may be superior to CT scanning for defining lung cancer spread in the thorax in specific situations. Because MRI can detect differences in intensity between tumor and normal tissues, including bone, soft tissues, fat, and vascular structures, it may be more accurate than CT scanning in delineating direct tumor invasion of the mediastinum, chest wall, diaphragm, or vertebral bodies.[13,88–91] This may be particularly useful in evaluating superior sulcus tumors or tumors abutting the mediastinum, structures of the chest wall, and diaphragm. However, most centers continue to rely on CT scanning as the noninvasive anatomic study of choice for evaluating potential mediastinal spread of lung cancer.

Recommendation

6. For patients with either a known or suspected lung cancer who are eligible for treatment, an MRI of the chest should not routinely be performed for staging the mediastinum. MRI may be useful in patients with NSCLC where there is concern for involvement of the superior sulcus or brachial plexus involvement. Grade of recommendation, 1B

The Search for Metastatic Disease

The purpose of extrathoracic scanning in patients with NSCLC is usually to detect metastatic disease,

especially at common metastatic sites such as the adrenal glands, liver, brain, and skeletal system, thereby sparing the patient fruitless radical treatment.[92] However, scans can only detect macroscopic metastatic deposits that have reached a size within the resolution capability of the imaging modality in question, and this can be considered a major shortcoming of all conventional tests currently used to detect distant metastases in patients with NSCLC. In more recent years, increasing attention has focused on the use of immunocytochemical techniques using monoclonal antibodies to detect occult micrometastases, which are sometimes associated with a worse prognosis, in the bone marrow of NSCLC patients.[93–98] Such techniques may add a new dimension to metastatic staging in the near future.

In the meantime, the preferred scans for staging patients with NSCLC in 2007 are CT scanning of the chest, CT scanning or MRI with contrast of the brain, and ^{99}Tc nuclear imaging of the skeletal system. The use of whole-body PET scans for extrathoracic staging is evolving, and PET scanning may ultimately play a significant role in the assessment of distant disease. The very limited extant data regarding whole-body single photon emission CT scanning for metastatic disease suggest that its performance is slightly inferior to that of PET scanning.[72,79]

It is clear that the use of extrathoracic scans must always be subordinate to a thoughtful overall clinical strategy for each individual patient. For example, a whole-body PET scan has little role in the diagnosis of a patient with clinically obvious, accessible advanced disease, such as skin metastases or massive hepatic replacement by metastatic tumor seen on CT scans.[53,54,99] In other circumstances, the need for tissue confirmation of metastatic disease can supercede the need for additional sophisticated scanning. For instance, in certain patients an adrenal biopsy, rather than a PET scan, may be required to clarify the nature of a unilateral adrenal mass seen on a CT scan.

It is well established that abnormal symptoms, physical examination findings, and routine blood tests in the initial clinical evaluation of patients with NSCLC are associated with a significant yield (approximately 50%) of abnormal scan findings.[92] Moreover, a rough semiquantitative relationship has been demonstrated in some studies[92,100] between the number of abnormal "clinical factors" and the frequency of abnormal scan findings. In the absence of all clinical factors, the scan yield is much lower, giving rise to the recommendation that scans be omitted in this setting,[31,48,100–104] though controversy persists on this point.[105] Other important variables focus on the primary lesion, since more scan abnormalities are associated with advanced thoracic lesions (T and N factors).[106,107] This is particularly true for patients with N2 disease, in whom asymptomatic metastases have been documented at a higher rate than would have been expected.[106,107] There has been some controversy with regard to cell type and the incidence of asymptomatic metastases. Several studies[108,109] have documented a higher incidence of brain metastases with adenocarcinomas as opposed to squamous cell cancers, but a large series[104] of patients with stage I and II lung cancer found no difference.

Several important caveats pertain to scanning for distant metastases in general. First is the issue of false-positive scan findings. Clinical entities that frequently give rise to false-positive scan findings include adrenal adenomas (present in 2 to 9% of the general population), hepatic cysts, degenerative joint disease, old fractures, and a variety of nonmetastatic space-taking brain lesions. When clinically indicated, additional imaging studies and/or biopsies are performed to establish the diagnosis, but complications and costs resulting from such subsequent investigations have received insufficient attention.[110,111] A second problem is that of false-negative scan findings (*ie*, metastases that are present but not picked up by current scanning techniques). This was demonstrated convincingly by Pagani,[112] who found metastatic NSCLC in 12% of radiologically normal adrenal glands by percutaneous biopsy; a more recent autopsy series[113] suggested that the sensitivity of CT scanning for adrenal metastases may be as low as 20%. A third difficulty is that most studies fail to carefully specify exactly which elements comprise the prescan clinical evaluation, or invoke differing clinical indicators to mandate scanning. Organ-specific findings such as headache and non-organ-specific complaints such as weight loss are both important.[100,114] The current preferred "expanded" clinical evaluation includes organ-specific and constitutional signs and symptoms, along with simple laboratory test results, as shown in Table 4.[92] Furthermore, Guyatt et al[115] have shown that careful delineation and quantification of historical features using a 5-point scale of severity can importantly affect the subsequent scan yield and ultimately the incidence of metastases after lung cancer surgery. A fourth issue is an ascertainment problem, since abnormal scan findings in many studies were not followed up with definitive biopsy proof of metastatic disease. This may relate to anatomic factors, overall debility, or refusal of the patient, or a variety of other cogent clinical concerns. Fifth, it must be noted that even biopsy proof of metastatic disease does not dictate a certain clinical management pathway. Carefully selected patients with localized lung cancers in

Table 4—*Clinical Findings Suggesting Metastatic Disease

Testing	Finding
Symptoms elicited in history	Constitutional: weight loss > 10 lb; and musculoskeletal: focal skeletal pain Neurological: headaches; syncope; seizures; extremity weakness; and recent changes in mental status
Signs found on physical examination	Lymphadenopathy (> 1 cm); hoarseness; superior vena cava syndrome; bone tenderness; hepatomegaly (> 13-cm span); focal neurologic signs, papilledema; and soft-tissue mass
Routine laboratory tests	Hematocrit: < 40% in men and 35% in women Elevated alkaline phosphatase, GGT, SGOT, and calcium levels

*GGT = γ-glutamyltransferase; SGOT = serum glutamic-oxaloacetic transaminase.

the thorax, accessible, solitary metastases to the brain or adrenal gland, and other favorable clinical features may obtain long-term survival with an aggressive treatment approach, including surgical extirpation of both the primary and metastatic site.[116,117] Finally, the lack of prospective randomized trials and outcome studies in the area of extrathoracic staging is striking. Two retrospective studies showed that scanning asymptomatic patients with early NSCLC did not help to predict recurrences postoperatively or to improve survival.[118,119] The only prospective randomized trial[120] showed no statistical difference in recurrence rates or survival in a group of patients who were randomized to undergo bone scintigraphy and CT scans of the head, liver, and adrenal glands, compared with the group assigned to undergo CT scans of the chest and mediastinoscopy, followed by thoracotomy when appropriate.

Utility of PET Scanning for Detecting Metastatic Disease

Since 1993, numerous studies have assessed the clinical utility of PET scans to assist in the search for metastatic disease in patients with NSCLC. In general, these tend to be relatively small, prospective, single-institution assessments in which whole-body PET scanning suggests the presence of unsuspected distant disease in 10 to 20% of cases.[20,27,121,122] The yield of unsuspected metastases depends on a number of factors, including whether PET scanning is gauged as an initial metastatic evaluation, or only after some metastases have already been detected via conventional scans.[42,123] The yield is higher in patients with clinical stage III disease,[79] and a relationship between thoracic nodal stage and PET scanning yield has been suggested.[124] When the area of interest is a single site (*eg*, adrenal glands or skeletal system), the performance characteristics (*ie*, sensitivity, specificity, PPV, NPV, and accuracy) of PET scanning are very favorable, often surpassing the performance of conventional imaging with CT scans or radionuclide bone imaging.[125,126] Furthermore, whole-body PET scanning enables the imaging of areas not covered in the traditional scanning algorithm, allowing the detection of occasional metastatic foci in, for example, skin, pelvis, skeletal muscle, soft tissue, kidney, and pancreas.[27] In most of these studies, abnormal PET scan findings are followed up with biopsy, serial conventional radiographs, and/or careful clinical assessment to confirm the veracity of the PET scan findings.

Nevertheless, several concerns pertain specifically to the emerging literature regarding PET scans as a test for distant disease. First, the exact criterion for a positive PET scan finding is usually based on an entirely subjective or semiquantitative comparison with background activity. Attempts to derive a reliable criterion based on standardized or differential uptake ratios have been generally unsuccessful to date. Second, several significant problems attend the use of PET scanning as an imaging modality for brain metastases. Not only does high baseline brain uptake pose a problem in detecting focal accumulations,[28] but many PET scanners include only the area from the base of the skull to the mid-thighs, thereby excluding much of the brain parenchyma from the images. Obtaining satisfactory brain PET scan images can require special equipment modifications and prolonged image-acquisition time.[20,127] Furthermore, the small size of most brain metastases may be problematic in terms of the limited resolution of conventional PET scans. Third, while there is some evidence that PET scanning can avert unnecessary thoracotomies,[80] improve clinical staging,[20,121,122,128] influence patient management decisions,[128] and alter radiotherapy planning,[79] there has been scant evidence to date linking PET scanning to an improvement in important patient outcomes such as recurrences of metastatic disease or mortality, and cost-effectiveness assessments are just beginning to emerge.[123,129,130] Fourth, a substantial ascertainment problem exists for negative PET scan findings, in that metastatic disease missed by PET scanning is generally unverifiable; thus, the false-negative rate is not truly knowable in most studies. But in one study,[131] 19% of patients who underwent a curative resection experienced a systemic relapse within a mean interval of 14 months despite a negative finding on a preoperative whole-body PET scan, suggesting that the false-negative problem may be significant. Finally, some of the larger, more recent

multiinstitutional studies[42] have shown substantially lower performance characteristics for PET scanning than those in the initial studies, with a PPV as low as 36% for metastatic disease.

To some extent, the very recent tempering of enthusiasm for PET scanning for distant disease likely reflects the usual trajectory of a new test, as greater experience accumulates in thousands of patients under a wide variety of clinical circumstances and interpretive expertise. In this sense, the experience with PET scanning echoes the experience with CT scanning of the mediastinum in patients with NSCLC, in which initial reports of sensitivity and specificity were in excess of 90%, before settling into the accepted values of 60 to 70% decades later. On the other hand, more recently introduced integrated PET/CT scanners offer the hope of combining metabolic imaging with precise anatomic resolution to further refine the search for metastatic disease.[58,84,132] In one highly publicized study,[58] integrated PET-CT scanning increased diagnostic certainty as to the precise location of metastasis in two of eight patients in whom conventional PET scanning detected unsuspected extrathoracic focal accumulations.

Thus, it is premature to definitively assess the role of whole-body PET scanning in the search for metastatic disease barely 10 years after its introduction into clinical practice. As of this writing, it appears that whole-body PET scanning is best suited to help resolve cases in which prior imaging of a possible metastatic deposit is equivocal, and to detect unsuspected distant metastasis in either the preoperative setting or in those patients who are at high risk for metastatic deposits even when they are clinically asymptomatic (clinical stage IIIA).[131]

Detection of Abdominal Metastases

Some PET scan studies can also be considered in the context of the scanning of individual organ systems in patients with NSCLC. Thirteen studies[105–107,109,133–141] evaluated the utility of clinical evaluation in detecting abdominal metastases in 1,291 patients using CT scanning as the reference standard (Table 5). Most of the studies limited study enrollment to patients with a negative clinical evaluation. In these nine studies,[107,109,133–137,139,140] the median prevalence of abdominal metastasis was 3% (range, 0 to 18%), and the median predictive value of a negative clinical evaluation was 97% (range, 82 to 100%). Four studies[105,106,138,141] enrolled patients with both positive and negative clinical evaluation findings. In these studies, the prevalence of abdominal metastasis ranged between 6% and 40%. Both sensitivity (range, 40 to 100%) and specificity (range, 27 to 65%) varied widely across studies. The use of CT scanning as an imperfect reference standard suggests that these estimates should be interpreted with caution.

It is relatively common to encounter adrenal masses on a routine CT scan, but many of these lesions are unrelated to the malignant process. A unilateral adrenal mass in a patient with NSCLC is more likely to be a metastasis than a benign lesion according to some studies,[92,142] but not others.[143,144] In the presence of clinical T1N0 NSCLC, adenomas predominate,[135,136] whereas adrenal metastases are

Table 5—*Utility of the Clinical Evaluation in Detecting Abdominal Metastases Using CT Scanning as the Reference Standard

Study/Year	Organ Scanned	Patients, No.	Routine Scan	Sensitivity	Specificity	PPV	NPV	Prevalence
Bilgin et al[105]/2002†	Liver	90	Yes	0.40	0.58	0.05	0.94	0.06
Miralles et al[141]/1993†	Liver	71	No	0.94	0.65	0.44	0.97	0.23
Silvestri et al[106]/1992	Adrenal	173	No	1.00	0.27	0.20	1.00	0.15
Ettinghausen et al[140]/1991	Adrenal	246	NR			‡	0.98	0.02
Salvatierra et al[109]/1990	Adrenal	146	Yes			‡	0.92	0.08
Grant et al[107]/1988	Liver, adrenal	114	Yes			‡	0.92	0.08
Whittlesey[139]/1988	Adrenal	180	Yes			‡	0.97	0.03
Mirvis et al[138]/1987	Liver, adrenal	72	Yes	0.90	0.58	0.59	0.89	0.40
Osada et al[137]/1987	Liver, adrenal	47	No			‡	1.00	0.00
Heavey et al[136]/1986	Adrenal	31	Yes, stage 1 disease			‡	0.97	0.03
Pearlberg et al[135]/1985	Liver, adrenal	23	Probably no			‡	1.00	0.00
Chapman et al[134]/1984	Adrenal	14	Yes			‡	0.86	0.14
Nielsen et al[133]/1982	Adrenal	84	Yes			‡	0.82	0.18
Summary		1,291		0.86 (0.62–0.96)	0.56 (0.25–0.93)	0.31	0.95	0.13

*See Table 2 for abbreviation not used in the text.

†Not included by Silvestri et al.[92]

‡PPV could not be estimated because the study evaluated with CT scanning only those patients in whom the clinical examination findings were negative.

frequently associated with large intrathoracic tumors or other extrathoracic metastases.[92,145] Many studies[140] have suggested that the size of a unilateral adrenal abnormality seen on a CT scan is an important predictor of metastatic spread, but this has not been a universal finding.

PET scans have performed exceptionally well in several studies specifically addressing the problem of adrenal metastases in NSCLC, with accuracy as high as 100% in two studies.[28,146] However, small lesions (< 15 mm) were underrepresented in these series, and other studies have noted rare false-positive findings in this site.[30,125,131]

Four possible approaches to distinguishing between malignant and benign adrenal masses have been proposed, as follows: evaluation by specific CT scanning or MRI criteria; evaluation with additional or serial imaging; evaluation by percutaneous biopsy; and evaluation by adrenalectomy. Well-defined, low-attenuation (fatty) lesions with a smooth rim on unenhanced CT scan are more likely to be benign adenomas,[147–149] but the CT scan appearance of many lesions is insufficiently distinctive.[147] Follow-up scanning with repeat CT, serial ultrasounds, MRI (especially with chemical shift and dynamic gadolinium-enhanced techniques[150]), 131-6-betaiodomethylnorcholesterol scanning,[151] or PET scanning can often help with the critical distinction between metastatic disease and adenoma. Percutaneous adrenal biopsy is a relatively safe and effective means of achieving a definitive diagnosis in doubtful cases, and is especially important when the histology of the adrenal mass will dictate subsequent management.[133,134] However, this procedure may be nondiagnostic or unfeasible due to anatomic constraints. When insufficient material results from a biopsy, repeat aspiration or even adrenalectomy should be considered.[140,147]

Most liver lesions are benign cysts or hemangiomas, but a contrast CT scan (or ultrasound) is often required to establish a likely diagnosis.[47] Percutaneous biopsy can be performed when diagnostic certainty is required. One metaanalysis[110] that specifically reviewed hepatic studies derived a pooled yield of 3% for liver metastases in asymptomatic patients with NSCLC. PET scanning can detect liver metastases with an accuracy of 92 to 100% and only rare false-positive findings, though data in patients with NSCLC are very limited at present.[20,28]

Detection of Brain Metastases

In most studies, the yield of CT scanning/MRI of the brain in NSCLC patients with negative clinical examination findings is 0 to 10%,[152–158] possibly ren-

Table 6—*Utility of the Clinical Evaluation in Detecting Brain Metastases Using Neuroimaging (CT Scanning/MRI/PET Scanning) as the Reference Standard*

Study/Year	Examination	Patients, No.	Routine Scan?	Sensitivity	Specificity	PPV	NPV	Prevalence
Bilgin et al[105]/2002*	Neurologic	90	No	0.50	0.56	0.15	0.88	0.13
Osada et al[31]/2001*	Neurologic	91	cT1-T2, < N2			†	0.98	0.02
Yokai et al[164]/1999*	Neurologic	155	Yes; CT scan			†	0.99	0.01
Cole et al[153]/1994*	Neurologic	42	No			†	1.00	0.00
Habets et al[163]/1992*	Neurologic	54	Yes	1.00	0.98	0.75	1.00	0.06
Kormas et al[158]/1992	Screening	157	N2 only			†	0.97	0.03
Salvatierra et al[109]/1990	Expanded	146	Adenocarcinoma and large cell cancer only	0.79	0.91	0.58	0.97	0.13
Grant et al[107]/1988	Screening	114	Yes			†	0.91	0.09
Osada et al[137]/1987	Screening	56	No			†	1.00	0.00
Crane et al[162]/1984	Neurologic	145	Yes	0.65	0.98	0.88	0.94	0.16
Hooper et al[100]/1984	Expanded	89	No	1.00	0.38	0.26	1.00	0.18
Levitan et al[161]/1984	Neurologic	55	Yes	0.73	1.00	1.00	0.91	0.27
Mintz et al[156]/1984	Neurologic	66	Yes	0.38	0.81	0.21	0.90	0.12
Tarver et al[108]/1984	Neurologic	323	Adenocarcinoma and SCLC only	0.83	0.78	0.64	0.91	0.32
Johnson et al[160]/1983	Neurologic	84	No	0.83	0.81	0.42	0.97	0.14
Jennings et al[159]/1980	Screening	102	NR			†	0.79	0.21
Butler et al[152]/1979	Screening	55	Yes			†	0.95	0.05
Jacobs et al[155]/1977	Screening	50	Yes			†	0.94	0.06
Summary		1,874		0.76 (0.61–0.87)	0.82 (0.69–0.91)	0.52	0.94	0.13

*Not included by Silvestri et al.[92]

†PPV could not be estimated because the study evaluated with neuroimaging only those patients in whom clinical examination findings were negative.

dering the test cost-ineffective.[154] Eighteen studies[31,100,105,107–109,137,152,153,155,156,158–164] evaluated the ability of clinical evaluation to detect brain metastases in comparison to CT in 1,830 patients (Table 6). Nine studies[31,107,137,152,153,155,158,159,164] limited enrollment to patients with a negative clinical evaluation. In these studies, the median prevalence of brain metastasis was 3% (range, 0 to 21%), and the median predictive value of a negative clinical evaluation finding was 97% (range, 79 to 100%). Nine other studies[100,105,108,109,156,160–163] enrolled patients with both positive and negative clinical evaluation findings. In these studies, the median prevalence of brain metastasis was higher (14%; range, 6 to 32%). The pooled sensitivity and specificity were 76% (95% CI, 61 to 87%) and 82% (95% CI, 69 to 91%), respectively.

An association among brain metastases, N2 disease in the chest, and adenocarcinoma histology has been described.[108,157,158] The rate of false-negative findings on CT scans wherein patients return with brain metastases within 12 months of the original scan is reported to be 3%.[158] False-positive scan results can be a problem in up to 11% of patients due to brain abscesses, gliomas, and other lesions[165]; therefore, biopsy may be essential in patients in whom management is critically dependent on the histology of the brain lesion.

MRI is more sensitive than CT scanning of the brain and picks up more lesions and smaller lesions,[166] but in some studies[164] this has not translated into a clinically meaningful difference in terms of survival. While studies show that MRI can identify additional lesions in patients with metastases, there are no studies that show that MRI is able to identify more patients with metastases from lung cancer compared to CT scanning. Therefore, CT scanning is an acceptable modality for evaluating patients for metastatic disease. If the primary lesion is more advanced than T1N0M0, MRI with contrast can identify asymptomatic, verifiable metastases to the brain in 22% of patients with NSCLC and surgically resectable thoracic disease.[167] However, the use of routine MRI in staging NSCLC patients with negative clinical evaluation findings has not been adequately studied to date; a role in patients with large cell carcinoma or stage III adenocarcinoma has been suggested.[168]

Many of the shortcomings of PET scans in imaging the brain have been alluded to. In addition, performance has been suboptimal, with sensitivity as low as 60%,[28] and occasional false-negative imaging findings of even sizable brain metastases.[169] One study[30] has suggested that PET scanning with ^{11}C-labeled choline may be far superior to the usual ^{18}F-FDG PET scanning for imaging brain metastases. In general, PET scanning is not considered to be reliable for detecting brain metastases.

Detection of Bone Metastases

The problem of false-positive scan abnormalities in radionuclide bone scintigraphy is particularly nettlesome, owing to the frequency of degenerative and traumatic skeletal damage and the difficulty in obtaining a definitive diagnosis via follow-up imaging or biopsy. False-positive bone imaging findings also occur with MRI, which may be no more accurate than nuclear bone imaging.[167] Eight studies examined the ability of the clinical evaluation to detect bone metastases in 723 patients using bone scanning as the reference standard (Table 7).[101–103,105,109,137,170,171] Two studies[102,137] limited enrollment to patients with negative clinical evaluation findings. In one study[102] that included patients with both SCLC and NSCLC, the prevalence and NPV were 16% and 84%, respectively. In a subsequent study[137] of patients with NSCLC, the prevalence and NPV were 30% and 70%, respectively. Six studies[101,103,105,109,170,171] enrolled patients with both positive and negative clin-

Table 7—*Utility of the Clinical Evaluation in Detecting Bone Metastases Using Radionuclide Bone Scanning as the Reference Standard*

Study/Year	Patients, No.	Histology	Routine Scan?	Sensitivity	Specificity	PPV	NPV	Prevalence
Bilgin et al[105]/2002	90	NSCLC	Yes	0.44	0.57	0.10	0.90	0.10
Michel et al[171]/1991	110	NSCLC	No	1.00	0.54	0.16	1.00	0.08
Tornyos et al[170]/1991	50	NSCLC	Yes	0.88	0.30	0.39	0.83	0.34
Salvatierra et al[109]/1990	146	NSCLC	No	0.79	0.88	0.50	0.97	0.13
Osada et al[137]/1987	66	NSCLC	Yes			*	0.70	0.30
Turner and Haggith[102]/1981	55	NSCLC/SCLC	No			*	0.84	0.16
Hooper et al[101]/1978	155	NSCLC/SCLC	No	0.90	0.40	0.36	0.92	0.27
Ramsdell et al[103]/1977	51	NSCLC	No	0.90	0.98	0.90	0.98	0.20
Summary	723			0.82 (0.57–0.94)	0.62 (0.32–0.85)	0.32	0.90	0.20

*PPV could not be estimated because the study evaluated with neuroimaging only those patients in whom the clinical examination findings were negative.

ical evaluation findings. In these studies, the median prevalence of bone metastasis was 16% (range, 8 to 27%), and the pooled sensitivity and specificity were 87% and 67%, respectively.

Using radionuclide bone scanning as the reference standard, the pooled negative predicted value of the clinical assessment was 90% (95% CI, 86 to 93%). The relatively high frequency of unsuspected positive scan findings has led some investigators[170] to recommend routine bone scanning in all preoperative patients. This concept is supported by the results of a study[172] in which 27% of asymptomatic patients were found to have skeletal metastases. False-negative findings on a bone scan can also be a problem, and in one series[171] skeletal metastases developed within 1 year in 6% of patients who had an initially negative bone scan result. PET scanning appears to have excellent performance characteristics in assessing bone metastases, with specificity, sensitivity, NPV, PPV, and accuracy all exceeding 90%,[28,126] though false-positive and false-negative findings are occasionally seen.[28,42,131] The accuracy of PET scanning surpassed that of radionuclide bone scanning in two direct comparative studies.[172,173]

Pleural/Lung Metastases

The limited data suggest that PET scanning can be useful in identifying lung metastases[28,174] and malignant pleural effusions[175,176] in NSCLC patients, though much of the data pertains to nonpulmonary malignancies. False-positive and false-negative findings have occasionally been noted.[30,175,177,178]

Recommendations

7. For patients with either a known or suspected lung cancer, a thorough clinical evaluation similar to that listed in Table 4 should be performed. Grade of recommendation, 1B

8. Patients with abnormal clinical evaluations should undergo imaging for extrathoracic metastases. Site-specific symptoms warrant a directed evaluation of that site with the most appropriate study (*eg*, head CT scanning/MRI plus either whole-body PET scanning or bone scanning plus abdominal CT scanning). Grade of recommendation, 1B

9. Routine imaging for extrathoracic metastases (*eg*, head CT scanning/MRI plus either whole-body PET scanning or bone scanning plus abdominal CT scanning) should be performed in patients with clinical stage IIIA and IIIB disease (even if they have negative clinical evaluation findings). Grade of recommendation, 2C

10. Patients with imaging study findings that are consistent with distant metastases should not be excluded from potentially curative treatment without tissue confirmation or overwhelming clinical and radiographic evidence of metastases. Grade of recommendation, 1B

Summary

CT scanning of the chest is useful in providing anatomic detail that better identifies the location of the tumor, its proximity to local structures, and whether or not lymph nodes in the mediastinum are enlarged. Unfortunately, the accuracy of chest CT scanning in differentiating benign from malignant lymph nodes in the mediastinum is unacceptably low. Whole-body PET scanning provides functional information on tissue activity, and has much better sensitivity and specificity than chest CT scanning for staging lung cancer in the mediastinum. In addition, distant metastatic disease can be detected by PET scanning. Still, positive findings on PET scans can occur as a result of nonmalignant etiologies (*eg*, infections), so tissue sampling to confirm suspected metastasis is usually required.

The clinical evaluation tool, that is, a thorough history and physical examination, remains the best predictor of distant metastatic disease. If the clinical evaluation finding is negative, then imaging studies such as CT scans of the head, bone scans, or abdominal CT scans are unnecessary and the search for metastatic disease is complete. If the signs, symptoms, or findings from the physical examination suggest malignancy, then sequential imaging, starting with the most appropriate study based on the clues obtained by the clinical evaluation, should be performed.

Abnormalities detected by any of the aforementioned imaging studies are not always cancer. Unless overwhelming evidence of metastatic disease is present on an imaging study, and where it will make a difference in treatment, all abnormal scan findings require tissue confirmation of malignancy so that patients are not denied the opportunity to have potentially curative treatment.

Summary of Recommendations

1. For patients with either a known or suspected lung cancer who are eligible for treatment, a CT scan of the chest with contrast including the upper abdomen (liver and adrenal glands) should be performed. Grade of recommendation, 1B

2. In patients with enlarged discrete mediastinal lymph nodes seen on CT scans (*ie*, > 1 cm on the short axis) and no evidence of metastatic disease, further evaluation of the mediastinum should be performed prior to definitive treatment of the primary tumor. Grade of recommendation, 1B

3. PET scanning to evaluate for mediastinal and extrathoracic staging should be considered in patients with clinical 1A lung cancer being treated with curative intent. Grade of recommendation, 2C

4. Patients with clinical 1B-IIIB lung cancer being treated with curative intent, should undergo PET scanning (where available) for mediastinal and extrathoracic staging. Grade of recommendation, IB

5. In patients with an abnormal result on FDG-PET scans, further evaluation of the mediastinum with sampling of the abnormal lymph node should be performed prior to surgical resection of the primary tumor. Grade of recommendation, 1B

6. For patients with either a known or suspected lung cancer who are eligible for treatment, an MRI of the chest should not be routinely performed for staging the mediastinum. MRI may be useful in patients with NSCLC in whom there is concern for involvement of the superior sulcus or brachial plexus. Grade of recommendation, 1B

7. For patients with either a known or suspected lung cancer, a thorough clinical evaluation similar to that listed in Table 4 should be performed. Grade of recommendation, 1B

8. Patients with abnormal clinical evaluation findings should undergo imaging for extrathoracic metastases. Site-specific symptoms warrant a directed evaluation of that site with the most appropriate study (*eg*, head CT scanning/MRI plus either whole-body PET scanning or bone scanning plus abdominal CT scanning). Grade of recommendation,1B

9. Routine imaging for extrathoracic metastases (*eg*, head CT scanning/MRI plus either whole-body PET scanning or bone scanning plus abdominal CT scanning) should be performed in patients with clinical stage IIIA and IIIB disease (even if they have a negative clinical evaluation finding). Grade of recommendation, 2C

10. Patients with imaging study findings that are consistent with distant metastases should not be excluded from potentially curative treatment without tissue confirmation or overwhelming clinical and radiographic evidence of metastases. Grade of recommendation, 1B

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