Noninvasive Staging of Non-small Cell Lung Cancer*

A Review of the Current Evidence

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Study objectives: **To determine the test performance characteristics of CT scanning, positron emission tomography (PET) scanning, MRI, and endoscopic ultrasound (EUS) for staging the mediastinum, and to evaluate the accuracy of the clinical evaluation (*ie*, symptoms, physical findings, or routine blood test results) for predicting metastatic disease in patients in whom non-small cell lung cancer or small cell lung cancer is diagnosed.**

Design, setting, and participants: **Systematic searches of MEDLINE, HealthStar, and Cochrane Library databases to July 2001, and of print bibliographies. Studies evaluating the staging results of CT scanning, PET scanning, MRI, or EUS, with either tissue histologic confirmation or long-term clinical follow-up, were included. The performance of the clinical evaluation was compared against the results of brain and abdominal CT scans and radionuclide bone scans.**

Measurement and results: **Pooled sensitivities and specificities for staging the mediastinum were as follows: for CT scanning: sensitivity, 0.57 (95% confidence interval [CI], 0.49 to 0.66); specificity, 0.82 (95% CI, 0.77 to 0.86); for PET scanning: sensitivity, 0.84 (95% CI, 0.78 to 0.89); specificity, 0.89 (95% CI, 0.83 to 0.93); and for EUS: sensitivity, 0.78 (95% CI, 0.61 to 0.89); specificity, 0.71 (95% CI, 0.56 to 0.82). For the evaluation of brain metastases, the summary estimate of the negative predictive value (NPV) of the clinical neurologic evaluation was 0.94 (95% CI, 0.91 to 0.96). For detecting adrenal and/or liver metastases, the summary NPV of the clinical evaluation was 0.95 (95% CI, 0.93 to 0.96), and for detecting bone metastases, it was 0.90 (95% CI, 0.86 to 0.93).**

Conclusions: **PET scanning is more accurate than CT scanning or EUS for detecting mediastinal metastases. The NPVs of the clinical evaluations for brain, abdominal, and bone metastases are ≥ 90%, suggesting that routinely imaging asymptomatic lung cancer patients may not be necessary. However, more definitive prospective studies that better define the patient population and improved reference standards are necessary to more accurately assess the true NPV of the clinical evaluation.** ***(CHEST 2003; 123:137S–146S)***

Key words: CT; lung neoplasms; meta-analysis; predictive value of tests; radiograph; sensitivity; specificity

Abbreviations: CI = confidence interval; EUS = endoscopic ultrasound; 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

Evaluation of patients with suspected lung cancer includes both a diagnosis of the primary tumor and an evaluation of the extent of spread to regional or distant lymph nodes or to other structures. The current system for staging lung cancer is based on the TNM classification.[1,2] The staging of lung cancer patients not only provides important prognostic information with regard to survival, but also guides the decision-making process with regard to the choosing optimal treatment modality.

Mediastinal lymph node involvement is found in 26% of newly diagnosed lung cancer patients, and extrathoracic metastases are found in 49%.[3] In patients with non-small cell lung cancer (NSCLC), those with mediastinal lymph node involvement are classified as having stage III disease, and those with extrathoracic metastases as having stage IV disease. For patients with small cell lung cancer (SCLC), both types of patients would be classified as having

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extensive disease. The remainder of newly diagnosed lung cancer patients who present without mediastinal lymph node or extrathoracic metastases are said to have stage I or II NSCLC or limited-stage SCLC.

The evaluation of a patient who presents with newly suspected lung cancer includes a clinical evaluation to assess for the presence or absence of extrathoracic metastatic disease and an imaging procedure to evaluate the mediastinum. As the most common sites of lung cancer metastases are the brain, bones, liver, and adrenal glands, the clinical evaluation ordinarily includes an assessment for headache, focal neurologic deficits, seizures, or changes in personality that may suggest brain metastases; bone pain or pathologic fractures that may suggest bone metastases; and abdominal or flank pain, or serum enzyme levels that may suggest liver metastases. Adrenal metastases are usually asymptomatic. Noninvasive imaging of the mediastinum may include the use of CT scanning, MRI, endoscopic ultrasound (EUS), or positron emission tomography (PET) scanning.

Materials and Methods

The purpose of the present study is twofold, as follows: (1) to assess the performance characteristics of noninvasive imaging procedures for staging the mediastinum; and (2) to assess the negative predictive value (NPV) of the clinical evaluation for predicting extrathoracic metastases. The NPV is the probability that a negative result correctly indicates the absence of metastatic disease.

Key Questions

The following two key questions were identified:

1. What are the sensitivities and specificities of CT scanning, MRI, EUS, and PET scanning for detecting malignant mediastinal lymph node involvement in lung cancer patients?
2. How accurate is the clinical evaluation (*ie*, symptoms, physical findings, or routine blood tests) for predicting metastatic disease among patients in whom lung cancer (*ie*, NSCLC or SCLC) has been diagnosed?

Search Strategy

Computerized searches of the MEDLINE bibliographic database (January 1991 to July 2001), HealthStar, and the Cochrane Library were performed. The decision to limit the search to the past 10 years was based on the evolution of technology after consultation with diagnostic radiologists at Duke University Medical Center. Key words used for the search included *lung neoplasm*, *bronchial neoplasm*, *neoplasm staging*, *neoplasm metastasis*, *lymphatic metastasis*, *CT*, *mediastinum radiography*, *emission-CT*, *adrenal gland neoplasms*, and *sensitivity and specificity*. In addition, we searched the reference lists of included studies, selected textbooks, practice guidelines, systematic reviews, and meta-analyses in order to ensure that all relevant studies were identified. Only articles that had been published in English were considered.

To address question 2, all articles described in a previously published meta-analysis evaluating tests for extrathoracic metastases also were included.[4]

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, NPV, and positive predictive value (PPV) of CT scanning, PET scanning, MRI, or EUS (question 1), or, for question 2, the raw data needed to calculate the NPV of the clinical evaluation. This last criterion was most important when analyzing studies that did not originally differentiate between hilar nodal involvement and mediastinal nodal involvement. Only articles meeting all five of these criteria were included.

Data Abstraction

Data were abstracted from included studies and tabulated separately by type of noninvasive test (*ie*, CT scan, PET scan, MRI, and EUS). Studies that evaluated the mediastinum by CT or PET scan were tabulated both by correlation to nodal station and by correlation to patient. Some studies described both hilar nodal involvement (stage N1) and mediastinal nodal involvement (stages N2 and N3). We considered only mediastinal nodal involvement (stages N2 and N3) as being *disease-positive* in analyzing the studies, which is consistent with the 1997 revision of the lung cancer staging system.[1] Patients with clinical or histopathologic stage IV disease were excluded from calculations of operating characteristics if the nodal stage was not described.

Either tissue histologic confirmation or, if that was unavailable, long-term (*ie*, ≥ 1 year) clinical outcome was utilized as the reference or "gold standard" by which imaging data were compared. If neither tissue pathologic confirmation nor clinical outcome was available, then the patient was deemed to be not evaluable and was excluded from further statistical analysis.

Data from studies that described the presence or absence of symptoms or signs of metastatic disease on clinical evaluation (*ie*, symptoms, physical examination findings, and laboratory evaluation results) were abstracted, with the presence or absence of extrathoracic metastases tabulated separately by the site of metastatic disease (*ie*, brain, abdomen, and bone). Positive findings on neuroimaging studies (*ie*, CT scan, MRI, or PET scan), abdominal CT scans, and radionuclide bone scans were used as references by which clinical evaluations for brain, abdominal, and bone metastases, respectively, were compared.

Statistical Analysis

Sensitivity is defined as the percentage of people with the disease who are detected by the test. It is calculated as the number of true-positive results divided by the sum of the number of true-positive results and false-negative results. *Specificity* is defined as the percentage of people without the disease who were correctly labeled by the test as not having the disease. It is calculated as the number of true-negative results divided by the sum of true-negative results and false-positive results. The *PPV* is defined as the likelihood that a patient with a positive test result actually has the disease. It is calculated as the number of true-positive results divided by the sum of true-positive results and false-positive results. The *NPV* is defined as the likelihood that a patient with a negative test result actually does not have the disease. It is calculated as the number or true-negative results divided by the sum of true-negative results and false-negative results. Both the PPV and the NPV vary with the prevalence of disease, which is the frequency of disease in the population. The prevalence can be calculated as the number of patients with either true-positive or false-negative results divided by the total number of patients.

Summary sensitivity and specificity, and their respective confidence intervals (CIs), were calculated using statistical software for the meta-analysis of diagnosis tests (Meta-Test; New England Cochrane Center; Boston, MA).[5] For studies that included patients with a positive and negative clinical evaluation, the sensitivity, specificity, and PPV of the evaluation for metastatic disease were calculated. As most studies of clinical evaluation included only asymptomatic patients, the primary outcome in these studies was the NPV.

We calculated NPVs using statistical software (FAST*PRO),[6] which tests individual study estimates for homogeneity and calculates a summary estimate of the NPV. Summary receiver operating characteristic (ROC) curves were generated for studies that provided information about patients with both positive and negative clinical evaluation results and for studies with tissue confirmation of disease.[7] As with conventional ROC curves, a summary ROC curve closer to the upper left-hand corner of the graph indicates better overall diagnostic test performance. To compare the summary ROC curves, a *t* test comparing the intercepts was performed using a Student *t* test.

Results

Although some studies analyzed results by nodal station, which may increase the correlation between imaging abnormalities and pathology, clinical decisions are made based on the accurate staging of multiple lymph-node stations in the mediastinum. We therefore present results at the patient level, not at the nodal-station level.

Mediastinal Staging by CT Scan

Twenty studies,[8–27] with 3,438 evaluable patients, evaluated the accuracy of standard CT scanning for staging the mediastinum (Table 1). All but three studies[16,17,27] used a > 10-mm short-axis diameter as the criterion for nodal positivity. The individual studies are plotted by sensitivity and 1 − specificity in Figure 1, which also displays the summary ROC curve. The pooled sensitivity of CT scanning was 0.57 (95% CI, 0.49 to 0.66), and the pooled specificity was 0.82 (95% CI, 0.77 to 0.86). However, there was marked heterogeneity in the sensitivity and specificity of the individual studies. The overall PPV and NPV of CT scanning for a patient were 0.56 (range, 0.26 to 0.84) and 0.83 (range, 0.63 to 0.93), respectively. The overall prevalence of mediastinal disease among the patients was 28% (range, 18 to 50%).

Mediastinal Staging by PET Scan

Staging the mediastinum by PET scanning was assessed by 18 studies[8,11,13,14,16–18,21,28–37] that included 1,045 evaluable patients from total of 1,166 enrolled patients (Table 2). In all studies, the imaging technique used ^{18}F-2-fluoro-2-deoxy-D-glucose

Table 1—*Accuracy of CT Scanning for Staging the Mediastinum in Lung Cancer Patients**

Study/Year	Patients, No.	CT Scan Technique	Sensitivity	Specificity	PPV	NPV	Prevalence
Dunagan et al[8]/2001	72	Contrast	0.50	0.87	0.56	0.84	0.25
Kamiyoshihara et al[9]/2001	546	Contrast	0.33	0.90	0.46	0.84	0.20
Osada et al[10]/2001	335	Contrast	0.56	0.93	0.77	0.83	0.30
Pieterman et al[11]/2000	102	Contrast	0.75	0.66	0.50	0.85	0.31
Takamochi et al[12]/2000	401	Contrast	0.30	0.82	0.30	0.83	0.20
Marom et al[13]/1999	79	Contrast	0.59	0.86	0.84	0.63	0.56
Saunders et al[14]/1999	84	NR	0.20	0.90	0.30	0.84	0.18
Suzuki et al[15]/1999	440	Contrast	0.33	0.92	0.56	0.82	0.23
Vansteenkiste et al[16]/1998	68	Contrast	0.75	0.63	0.58	0.78	0.41
Vansteenkiste et al[17]/1998	56	Contrast	0.86	0.79	0.80	0.85	0.50
Bury et al[18]/1997	64	Contrast	0.79	0.84	0.58	0.93	0.22
Gdeedo et al[19]/1997	100	Contrast	0.63	0.57	0.41	0.76	0.32
Buccheri et al[20]/1996	80	Contrast	0.64	0.74	0.48	0.84	0.28
Bury et al[21]/1996	53	Contrast	0.71	0.81	0.63	0.85	0.32
Aaby et al[22]/1995	57	NR	0.72	0.91	0.86	0.81	0.44
Primack et al[23]/1994	159	Contrast	0.63	0.86	0.73	0.79	0.38
Yokoi et al[24]/1994	113	Contrast	0.62	0.80	0.61	0.81	0.33
McLoud et al[25]/1992	143	Contrast	0.64	0.62	0.44	0.79	0.31
Jolly et al[26]/1991	336	Contrast	0.71	0.86	0.69	0.87	0.30
Cole et al[27]/1993	150	NR	0.26	0.81	0.26	0.81	0.21
Summary	3,438		0.57	0.82	0.56	0.83	0.28

*NR = not reported.

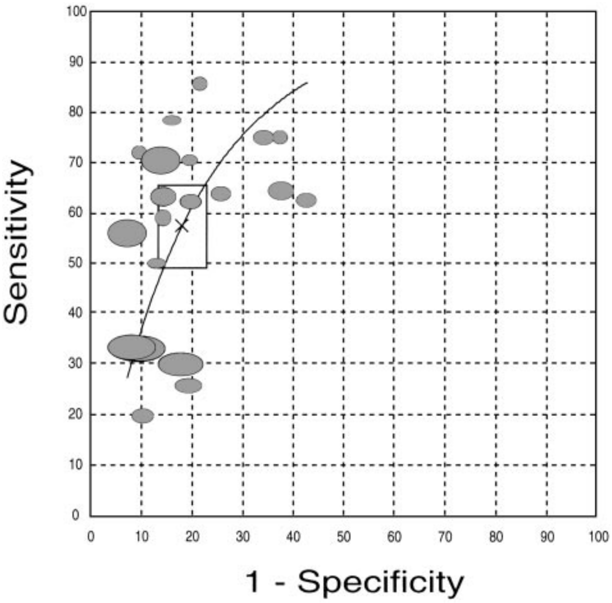

FIGURE 1. Summary ROC curve for imaging mediastinal lymph nodes that are > 1 cm diameter with standard CT scanning. The gray ellipses indicate individual study estimates of sensitivity and 1 − specificity. A study showing the highest accuracy will appear in the top left corner of the graph. The size of the gray ellipse is proportional to the statistical weight of the study in the analysis (roughly proportional to its size). The "X" indicates the summary point estimates for sensitivity and 1 − specificity from meta-analyses of sensitivity and specificity, independent of one another. The outlined box indicates 95% CIs about the summary sensitivity and 1 − specificity estimates. The dark line represents the summary ROC curve.

as the positron emitter. The individual studies are plotted by sensitivity and 1 − specificity in Figure 2, which also displays the summary ROC curve. As compared with the CT scanning summary ROC curve, the PET scanning summary ROC curve was significantly more accurate ($t = 19$; $p < 0.001$). The pooled sensitivity was 0.84 (95% CI, 0.78 to 0.89), and the pooled specificity was 0.89 (95% CI, 0.83 to 0.93). The heterogeneity was less than that found among the studies of CT scanning. The overall PPV and NPV were 0.79 (range, 0.40 to 1.00) and 0.93 (range, 0.75 to 1.00), respectively. The overall prevalence of mediastinal disease was 32% (range, 5 to 56%).

Mediastinal Staging by CT and PET Scans Combined

Three studies,[16,17,31] including 152 patients total, evaluated the mediastinum with both CT and PET scanning. The sensitivity of the combined tests ranged from 0.78 to 0.93, and the specificity ranged from 0.82 to 0.95. The PPV ranged from 83 to 93%, and the NPV ranged from 88 to 95%. The prevalence of mediastinal disease ranged from 32 to 50%.

Mediastinal Staging by MRI Scan

One study[38] of 20 patients assessed the accuracy of MRI for staging the mediastinum with and without gadolinium enhancement. With gadolinium, the sensitivity was 1.0, the specificity was 0.91, the PPV was 0.96, and the NPV was 1.0. Without gadolinium, the sensitivity dropped to 0.63, the specificity improved to 1.0, the PPV improved to 1.0, and the NPV fell to 0.55.

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

Study/Year	Patients, No.	Sensitivity	Specificity	PPV	NPV	Prevalence
Dunagan et al[8]/2001	81	0.52	0.88	0.61	0.84	0.26
Farrell et al[28]/2000	84	1.00	0.93	0.40	1.00	0.05
Liewold et al[29]/2000	78	0.93	0.78	0.69	0.95	0.35
Pieterman et al[11]/2000	102	0.91	0.86	0.74	0.95	0.31
Roberts et al[30]/2000	100	0.88	0.91	0.75	0.96	0.24
Magnani et al[31]/1999	28	0.67	0.84	0.67	0.84	0.32
Marom et al[13]/1999	79	0.73	0.94	0.85	0.88	0.56
Saunders et al[14]/1999	84	0.71	0.97	0.86	0.93	0.20
Vansteenkiste et al[16]/1998	68	0.93	0.95	0.93	0.95	0.41
Vansteenkiste et al[17]/1998	56	0.86	0.43	0.60	0.75	0.50
Bury et al[18]/1997	64	0.86	1.0	1.0	0.96	0.22
Guhlmann et al[32]/1997	32	0.87	1.0	1.0	0.89	0.47
Steinert et al[33]/1997	47	0.92	0.97	0.92	0.97	0.28
Bury et al[21]/1996	30	0.88	0.86	0.88	0.86	0.53
Sazon et al[34]/1996	32	1.00	1.00	1.00	1.00	0.50
Scott et al[35]/1996	27	1.00	1.00	1.00	1.00	0.33
Chin et al[36]/1995	30	0.78	0.81	0.64	0.89	0.30
Wahl et al[37]/1994	23	0.82	0.75	0.75	0.82	0.48
Summary	1,045	0.84	0.89	0.79	0.93	0.32

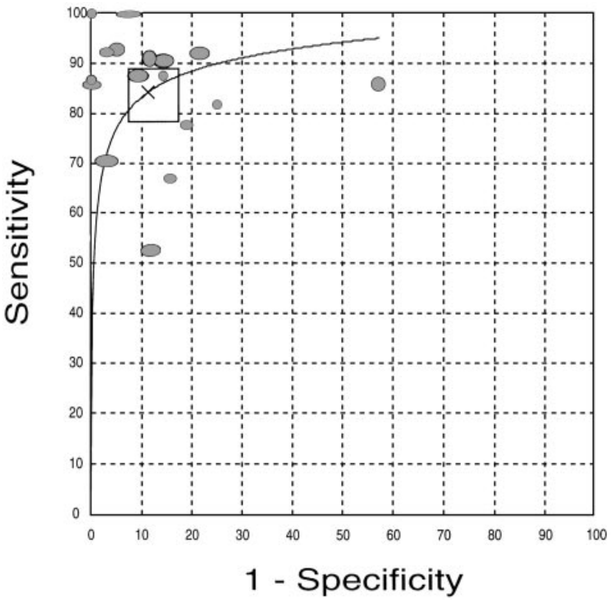

FIGURE 2. Summary ROC curve for imaging mediastinal lymph nodes that are > 1 cm diameter with PET using ^{18}F-2-fluoro-2-deoxy-D-glucose. The gray ellipses indicate individual study estimates of sensitivity and 1 − specificity. The size of the gray ellipse is proportional to the weight of the study in the analysis. The "X" indicates the summary point estimates for sensitivity and 1 − specificity from meta-analyses of sensitivity and specificity, independent of one another. The outlined box indicates 95% CIs about the summary sensitivity and 1 − specificity estimates. The dark line represents the summary ROC curve.

Mediastinal Staging by EUS

Five studies[39–43] assessed the use of EUS to stage the mediastinum in 163 evaluable patients (Table 3). The size of the lymph node and evidence of necrosis (*ie*, *echo heterogeneity*) or capsular disruption (*ie*, *irregularity of shape*) provided criteria with which to determine the presence of metastases. The pooled sensitivity of EUS was 0.78 (95% CI, 0.61 to 0.89), and the pooled specificity of EUS was 0.71 (95% CI, 0.56 to 0.82). The overall PPV was 75% (range, 38 to 100%), and the overall NPV was 79% (range, 57 to 89%). The overall prevalence of mediastinal involvement in these patients was 50% (range, 25 to 76%).

Detection of Brain Metastases by Clinical Evaluation

Seventeen studies[10,44–59] were included that evaluated the ability of clinical evaluation to detect brain metastases in 1,784 patients (Table 4). Eight studies[46,48,51–56] provided information on patients with both positive and negative clinical evaluations, while nine studies[10,44,45,47,49,50,57–59] included only patients with a negative clinical evaluation findings. One study[44] used both CT scanning and MRI as the reference standard in two separate analyses. Only the results from the CT scan analysis are considered here.

The NPV of the clinical neurologic evaluation ranged from 0.79 to 1.00, but there was significant heterogeneity. The calculated summary estimate for the NPV was 0.94 (95% CI, 0.91 to 0.96). For studies that evaluated patients with both positive and negative clinical evaluations (n = 8), the pooled sensitivity was 0.76 (95% CI, 0.64 to 0.84), and the pooled specificity was 0.87 (95% CI, 0.74 to 0.94). The PPV was 0.54, with a range of 0.21 to 1.00. The overall prevalence of brain metastases in these patients was 13% (range, 0 to 32%).

Detection of Abdominal Metastases by Clinical Evaluation

Twelve studies[48–50,60–68] assessed the ability of the clinical evaluation to detect adrenal and/or liver metastases in 1,201 patients (Table 5). Three of the studies[60,61,64] evaluated both symptomatic (including abnormal liver function tests as the only symptom) and asymptomatic patients, while nine studies[48–50,62,63,65–68] included only negative clinical evaluation patients. There was heterogeneity in the NPV, which ranged from 0.82 to 1.0. The calculated summary estimate was 0.95 (95% CI, 0.93 to 0.96). For studies that evaluated patients who had a negative and a positive clinical evaluation (n = 3), the pooled sensitivity and specificity of clinical abdominal evaluation for detecting abdominal metastases were 0.92 (95% CI, 0.82 to 0.97) and 0.49 (95% CI, 0.25 to 0.74), respectively. The PPV ranged from 0.20 to 0.59, with a mean of 0.32. The overall prevalence of abdominal metastases was 10% (range, 0 to 40%).

Detection of Bone Metastases by Clinical Evaluation

Seven studies[48,50,69–73] assessed the ability of clinical evaluation to detect bone metastases in 633 patients (Table 6). All but two studies[50,71] included both symp-

Table 3—*Accuracy of EUS Without Biopsy for Staging the Mediastinum in Lung Cancer Patients*

Study/Year	Patients, No.	Sensitivity	Specificity	PPV	NPV	Prevalence
Wiersema et al[39]/2001	29	0.86	0.57	0.86	0.57	0.76
Gress et al[40]/1997	45	0.86	0.83	0.83	0.86	0.49
Potepan et al[41]/1996	30	0.45	0.58	0.38	0.65	0.37
Silvestri et al[42]/1996	27	0.89	1.00	1.00	0.82	0.67
Schuder et al[43]/1991	32	0.75	0.71	0.46	0.89	0.25
Summary	163	0.78	0.71	0.75	0.79	0.50

Table 4—*Utility of the Clinical Evaluation in Detecting Brain Metastases Using Neuroimaging (CT Scanning, MRI, and PET Scanning) as the Reference Standard**

Study/Year	Examination	Patients, No.	Routine Scan?	Sensitivity	Specificity	PPV	NPV	Prevalence
Osada et al[10]†/2001	Neuro	91	cT1–T2, < N2			‡	0.98	0.02
Yokoi et al[44]†/1999	Neuro	155	Yes; CT			‡	0.99	0.01
Cole et al[45]†/1994	Neuro	42	No			‡	1.00	0.00
Habets et al[46]†/1992	Neuro	54	Yes	1.00	0.98	0.75	1.00	0.06
Kormas et al[47]/1992	Screening	157	N2 only			‡	0.97	0.03
Salvatierra et al[48]/1990	Expanded	146	Adenocarcinoma and large cell only	0.79	0.91	0.58	0.97	0.13
Grant et al[49]/1988	Screening	114	Yes			‡	0.91	0.09
Osada et al[50]/1987	Screening	56	No			‡	1.00	0.00
Crane et al[51]/1984	Neuro	145	Yes	0.65	0.98	0.88	0.94	0.16
Hooper et al[52]/1984	Expanded	89	No	1.00	0.38	0.26	1.00	0.18
Levitan et al[53]/1984	Neuro	55	Yes	0.73	1.00	1.00	0.91	0.27
Mintz et al[54]/1984	Neuro	66	Yes	0.38	0.81	0.21	0.90	0.12
Tarver et al[55]/1984	Neuro	323	Adenocarcinoma and SCLC only	0.83	0.78	0.64	0.91	0.32
Johnson et al[56]/1983	Neuro	84	No	0.83	0.81	0.42	0.97	0.14
Jennings et al[57]/1980	Screening	102	NR			‡	0.79	0.21
Butler et al[58]/1979	Screening	55	Yes			‡	0.95	0.05
Jacobs et al[59]/1977	Screening	50	Yes			‡	0.94	0.06
Summary		1,784		0.76	0.87	0.54	0.94	0.13

*Neuro = neurological; NR = not reported.
†Not included by Silvestri et al.[4]
‡PPV could not be estimated because study evaluated with neuroimaging only those patients in whom the clinical examination findings were negative.

tomatic and asymptomatic patients. The pooled sensitivity and specificity of clinical bone evaluation for detecting bone metastases were 0.87 (95% CI, 0.79 to 0.93) and 0.67 (95% CI, 0.40 to 0.88), respectively. There was heterogeneity in the NPV, with a calculated summary estimate of 0.90 (95% CI, 0.86 to 0.93) and a range of 0.70 to 1.0. The mean PPV was 0.36 (range, 0.16 to 0.90). The overall prevalence of bone metastases was 20% (range, 8 to 34%).

Discussion

Patients presenting with newly diagnosed lung cancer need to be assessed for potential mediastinal

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
Miralles et al[60]†/1993	Liver	71	No	0.94	0.65	0.44	0.97	0.23
Silvestri et al[61]/1992	Adrenal	173	No	1.00	0.27	0.20	1.00	0.15
Ettinghausen and Burt[62]/1991	Adrenal	246	NR			‡	0.98	0.02
Salvatierra et al[48]/1990	Adrenal	146	Yes			‡	0.92	0.08
Grant et al[49]/1988	Liver, adrenal	114	Yes			‡	0.92	0.08
Whittlesey[63]/1988	Adrenal	180	Yes			‡	0.97	0.03
Mirvis et al[64]†/1987	Liver, adrenal	72	Yes	0.90	0.58	0.59	0.89	0.40
Osada et al[50]/1987	Liver, adrenal	47	No			‡	1.00	0.00
Heavey et al[65]/1986	Adrenal	31	Yes, stage 1			‡	0.97	0.03
Pearlberg et al[66]/1985	Liver, adrenal	23	Probably no			‡	1.00	0.00
Chapman et al[67]/1984	Adrenal	14	Yes			‡	0.86	0.14
Nielsen et al[68]/1982	Adrenal	84	Yes			‡	0.82	0.18
Summary		1,201		0.92	0.49	0.32	0.95	0.10

*See Table 1 for abbreviation not used in the text.
†Not included by Silvestri et al.[4]
‡PPV could not be estimated because study evaluated with CT scanning only those patients in whom the clinical examination findings were negative.

Table 6—*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
Michel et al[69]/1991	110	NSCLC	No	1.00	0.54	0.16	1.00	0.08
Tornyos et al[70]/1991	50	NSCLC	Yes	0.88	0.30	0.39	0.83	0.34
Salvatierra et al[48]/1990	146	NSCLC	No	0.79	0.88	0.50	0.97	0.13
Osada et al[50]/1987	66	NSCLC	Yes			*	0.70	0.30
Turner and Haggith[71]/1981	55	NSCLC/SCLC	No			*	0.84	0.16
Hooper et al[72]/1978	155	NSCLC/SCLC	No	0.90	0.40	0.36	0.92	0.27
Ramsdell et al[73]/1977	51	NSCLC	No	0.90	0.98	0.90	0.98	0.20
Summary	633			0.87	0.67	0.36	0.90	0.20

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

and extrathoracic metastases. When selecting a test for staging the disease of a patient with known or suspected lung cancer, two issues need to be considered. First, one needs to select a test that will assess the patient for metastatic disease. This test should have a high sensitivity and specificity. Second, one needs to be able to interpret accurately the test results for an individual patient. For example, what is the likelihood that a negative test result means a patient is free of metastatic disease or, conversely, that a positive test confirms metastatic disease? This issue is addressed by the PPVs and NPVs of a test. However, the NPV and PPV of a test are affected by the prevalence of disease. Thus, patients may be approached differently depending on one's initial degree of suspicion regarding mediastinal or extrathoracic involvement. A patient suspected of having metastases would require a test with high sensitivity to confirm the diagnosis. In contrast, a patient suspected of having early-stage disease would require a test with high specificity to rule out advanced disease. Determining the most expeditious and cost-effective method of doing this has been the focus of considerable research.[4,74–78]

The present meta-analysis suggests that PET scanning of the mediastinum is more sensitive and specific than either CT scanning or EUS alone. A comparison of the summary ROC curves demonstrates greater accuracy for PET scanning than for CT scanning, with a negative PET scan providing a $> 90\%$ certainty of the absence of positive mediastinal lymph node metastases. These findings are compatible with those of Dwamena et al,[77] who also demonstrated the superiority of PET scanning to CT scanning for detecting mediastinal nodal metastases. Other studies[11] have demonstrated improved sensitivity and specificity for PET scanning vs CT scanning and have shown that $> 60\%$ of patients have a resultant change in their clinical stage when using PET scanning vs CT scanning for staging. Additionally, a randomized trial comparing a conventional workup (*ie*, invasive diagnostic and therapeutic procedures) alone vs PET scanning followed by a conventional workup identified more patients in the PET scan group with mediastinal and distant metastases, and subsequently fewer patients who underwent futile thoracotomies.[79] EUS without biopsy is limited in that it cannot image all nodal stations, and its sensitivity and specificity are lower than those for PET scanning

Our meta-analysis of CT scanning demonstrated that the accuracy of CT scanning for mediastinal staging has not improved over the past decade, despite improvements in CT scan resolution. The sensitivity and specificity of CT scanning in our analysis were not significantly better than those in a meta-analysis of studies performed between 1980 and 1988,[80] with sensitivities of 57% vs 79%, respectively, and specificities of 82% vs 78%, respectively.

Although only three studies,[16,17,31] which had small sample sizes, have evaluated the performance characteristics of combined CT and PET scanning for mediastinal staging, the combination of the two imaging tests may achieve greater staging accuracy than either test alone. A cost-effectiveness analysis utilizing PET scanning for all patients who had node-negative CT scan results was encouraging, demonstrating that the cost of PET scanning was nearly compensated for by the more appropriate selection of patients for beneficial surgery.[78] Future studies should include the evaluation of a combination of CT and PET scanning in prospective clinical trials. Furthermore, the ongoing development of fusion scanners that combine CT and PET warrants clinical trials and may provide an optimal method for noninvasive clinical staging.

The present meta-analysis also updates the meta-analysis performed by Silvestri et al[4] As with his study, we found the calculated summary estimates for the NPV to be $\geq 90\%$ for the clinical evaluation of asymptomatic patients for brain, abdominal, or bone metastases. These findings are consistent with the findings of a retrospective analysis[75] of 755 patients with clinical stage T1-2N0, which found only five sites of silent metastasis after extensive imaging for extrathoracic disease in all presenting patients. However, within the studies combined in our meta-analyses, there was considerable heterogeneity with respect to their individual NPV. The greatest range was found for the evaluation for bone metastases, in which the NPVs ranged from 0.7 to 1.0. Some of the heterogeneity may be due to the imperfect reference standard, in which abnormal bone scan findings were not followed up with histologic confirmation of disease. For example, in the study in which 30% of patients had a false-negative clinical evaluation,[50] only 4 of 17 patients with abnormal bone scan findings received confirmations of lung cancer that was metastatic to bone. There was also significant variation in the stage and cell type of disease in the patients who were evaluated in the included studies. For the evaluation of abdominal metastases, the NPVs also ranged broadly between 0.82 and 1.0. In this case, (1) the studies did not control for stage and/or size of the primary tumor, (2) the reference standard was suboptimal, as abnormal findings on CT scanning were not always confirmed with biopsy, and (3) patient populations varied between studies. For the evaluation of brain metastases, with the exception of one very poorly designed study,[57] the NPV, although heterogeneous, ranged more narrowly between 0.91 and 1.0.

In contrast, although the PPV varied among the studies included in this meta-analysis of the clinical evaluation for detecting metastatic disease, the resultant following conclusion remains the same: further diagnostic testing is necessary to confirm the presence of disease in patients with abnormal findings on clinical evaluation.

A separate issue that was not evaluated by this meta-analysis is the role that whole-body PET scanning may play in the workup of asymptomatic patients for metastatic disease. A recent randomized trial[79] suggests that the addition of PET scanning to a conventional workup identified more patients with distant metastases among those with suspected NSCLC.

There are limitations to the present meta-analysis. No attempt was made to obtain unpublished data or non-English-language studies. An evaluation of performance characteristics by cell type and/or stage was not possible, but such data, if available, may be useful for assessing the optimal staging criteria for different tumor types.

In summary, the clinical evaluation of a newly diagnosed lung cancer patient suggests that PET is more accurate for detecting mediastinal metastases than the standard assessment with CT chest scanning. Future studies should be performed to determine the role of combined PET and CT scanning or to delineate which patients should undergo PET scanning after undergoing a CT scan. Future technologic advancements, such as the development of a single-modality scanner that performs the role of both a CT and PET scanner, may provide a more accurate and cost-effective approach. However, this would need to be validated in prospective clinical trials.

This update of the meta-analysis performed by Silvestri et al[4] suggests that the clinical evaluation of patients who present without symptoms of metastatic disease may obviate the need for brain, abdominal, and bone imaging to detect distant metastases. However, more definitive prospective studies that clearly define the patient population, including cell type and stage, that address the issue of patient referral bias, and that provide improved reference standards with histologic confirmation of positive findings are necessary to more accurately assess the true NPV of the clinical examination. Moreover, the role of whole-body PET scanning for evaluating mediastinal and extrathoracic metastases remains to be studied.

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