PREOPERATIVE STAGING OF NON–SMALL-CELL LUNG CANCER WITH POSITRON-EMISSION TOMOGRAPHY

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ABSTRACT

Background Determining the stage of non–small-cell lung cancer often requires multiple preoperative tests and invasive procedures. Whole-body positron-emission tomography (PET) may simplify and improve the evaluation of patients with this tumor.

Methods We prospectively compared the ability of a standard approach to staging (computed tomography [CT], ultrasonography, bone scanning, and, when indicated, needle biopsies) and one involving PET to detect metastases in mediastinal lymph nodes and at distant sites in 102 patients with resectable non–small-cell lung cancer. The presence of mediastinal metastatic disease was confirmed histopathologically. Distant metastases that were detected by PET were further evaluated by standard imaging tests and biopsies. Patients were followed postoperatively for six months by standard methods to detect occult metastases. Logistic-regression analysis was used to evaluate the ability of PET and CT to identify malignant mediastinal lymph nodes.

Results The sensitivity and specificity of PET for the detection of mediastinal metastases were 91 percent (95 percent confidence interval, 81 to 100 percent) and 86 percent (95 percent confidence interval, 78 to 94 percent), respectively. The corresponding values for CT were 75 percent (95 percent confidence interval, 60 to 90 percent) and 66 percent (95 percent confidence interval, 55 to 77 percent). When the results of PET and CT were adjusted for each other, only PET results were positively correlated with the histopathological findings in mediastinal lymph nodes ($P<0.001$). PET identified distant metastases that had not been found by standard methods in 11 of 102 patients. The sensitivity and specificity of PET for the detection of both mediastinal and distant metastatic disease were 95 percent (95 percent confidence interval, 88 to 100 percent) and 83 percent (95 percent confidence interval, 74 to 92 percent), respectively. The use of PET for clinical staging resulted in a different stage from the one determined by standard methods in 62 patients: the stage was lowered in 20 and raised in 42.

Conclusions PET improves the rate of detection of local and distant metastases in patients with non–small-cell lung cancer. (N Engl J Med 2000; 343:254-61.)

THE occurrence of distant metastases and metastases to mediastinal lymph nodes profoundly affects the prognosis of non–small-cell lung cancer, making accurate staging crucial for selecting appropriate treatment. When used alone, the results of most staging methods, such as computed tomography (CT), ultrasonography, and radionuclide bone scanning, are far from ideal. Whole-body positron-emission tomography (PET) with ^{18}F-fluorodeoxyglucose (fludeoxyglucose F 18) as a tracer is a new metabolic imaging technique that relies on the fact that there is increased metabolism of glucose in tumor cells.[1,2] Pulmonary tumors actively metabolize the tracer, and several studies have shown that the method has about 95 percent sensitivity for detecting primary bronchial tumors[3,4] and mediastinal lymph-node metastases.[5-7] Within the body, the method has a lower limit of resolution of 1 to 1.2 cm. The specificity of this method is not optimal, because the uptake of ^{18}F-fluorodeoxyglucose is increased by the presence of inflammatory processes in the lungs. Another limitation is that histopathological verification of the results of the PET scan is often conducted only on "hot spots" (areas in which the uptake of ^{18}F-fluorodeoxyglucose is much greater than the background uptake in all areas but the heart, brain, and urinary tract) and does not include lymph nodes whose uptake of the radioactive glucose is not increased. The use of PET to identify distant metastases in patients with non–small-cell lung cancer has been investigated in a few small studies.[8,9] Therefore, we prospectively investigated the role of PET in evaluating the mediastinum and detecting distant metastases in such patients.

METHODS

Patients

Patients with potentially resectable non–small-cell lung cancer who were being evaluated with standard tests and procedures in the outpatient department of pulmonary diseases at Groningen University Hospital in Groningen, the Netherlands, were eligible for the study. Patients were excluded if they had hyperglycemia (defined as a serum glucose level of more than 180 mg per deciliter [10 mmol per liter]) before the PET study, since in a pilot study, such levels seemed to affect the quality of the PET images

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adversely, or had undergone cervical mediastinoscopy or parasternal mediastinotomy. All patients were evaluated by means of a history taking, physical examination, blood count, measurement of electrolytes, tests of renal and liver function, bronchoscopy, cervical mediastinoscopy, and CT of the chest, including the upper abdomen. In patients with symptoms or signs suggestive of distant metastases, appropriate additional imaging tests and biopsies were performed. The combination of tests and invasive procedures leading to clinical classification according to the tumor–node–metastasis (TNM) staging system of the American Joint Committee on Cancer[10] was considered traditional staging. Every two months for at least six months after thoracotomy, the patients underwent a physical examination and chest radiography (as well as additional tests in patients suspected of having distant metastases).

All patients gave written informed consent. The study was approved by the medical ethics committee of Groningen University Hospital.

Surgery

Cervical mediastinoscopies, parasternal mediastinotomies, and explorative thoracotomies were performed by four thoracic surgeons. Cervical mediastinoscopy was considered adequate when it included, at a minimum, biopsy specimens of the paratracheal and tracheobronchial lymph nodes on the right and left sides, and subcarinal lymph nodes. Mediastinal lymph nodes were dissected during thoracotomy, with thorough attention paid to the superior and inferior lymph nodes on the right side or the superior and inferior mediastinal and aortic lymph nodes on the left. Surgeons were strongly encouraged to dissect both normal-appearing lymph nodes and those that appeared enlarged on CT. Lymph nodes were labeled according to the classification of Mountain and Dresler[11] and sent for histopathological examination, which included staining with hematoxylin and eosin.

Whole-Body PET

PET was performed with a scanner (ECAT model 951/31, Siemens/CTI, Knoxville, Tenn.) that had a field of view of 10.8 cm and a full width of 6 mm at half-maximal resolution. Data were reconstructed iteratively[12] into coronal, sagittal, and transverse sections and a three-dimensional rotating projection. ^{18}F-fluorodeoxyglucose was synthesized according to the method of Hamacher et al.[13] by a high-performance liquid chromatography controlled-synthesis module.[14] Patients were instructed to fast for six hours before the PET study, but they were allowed to drink water and to take their usual medications. ^{18}F-fluorodeoxyglucose (370 MBq) was administered intravenously.

Before the prospective study, we performed a pilot study in seven patients with non–small-cell lung cancer to determine the optimal scanning protocol, especially with regard to the mediastinum. Static (i.e., isolated rather than dynamic) emission scans were performed 30, 60, 90, and 120 minutes after the injection of ^{18}F-fluorodeoxyglucose. Imaging reconstruction was performed after 2.5, 5, 8, and 10 minutes in each position for both emission scans (which measure only ^{18}F-fluorodeoxyglucose uptake) and transmission scans (source, germanium-68). The results of post-emission transmission scans were used to correct for attenuation of the ^{18}F-fluorodeoxyglucose signal. The emission scans performed 90 minutes after the injection of ^{18}F-fluorodeoxyglucose, with reconstructions made after eight minutes in each position, were considered to have provided the best images with respect to the extent of contrast between hot spots and the background level in mediastinal lymph-node levels. Both types of scans were performed from the level of the first cervical vertebra to the level of the fifth lumbar vertebra. All clinicians involved in the care of the patients were unaware of the results of PET.

CT of the Chest

CT of the chest and upper abdomen including the adrenal glands was performed with a 120-KV, 125-mA tomoscan (model SR 7000, Philips Medical Systems, Enthoven, the Netherlands) with a slice thickness of 10 mm and a scanning time of one second per slice. During CT, 200 ml of contrast medium (Omnipaque, iohexol, Nycomed, Amersham, Princeton, N.J.) was administered intravenously at a rate of 1.5 ml per second. In 13 patients no contrast medium was used.

Assessment of Metastases

Hot Spots inside the Mediastinum

A positive PET scan was one that had at least one hot spot. All imaging studies were analyzed by two independent observers who were not aware of the patients' clinical data. If they could not reach a consensus, the opinion of a third observer was sought.

The gold standard for the diagnosis of mediastinal metastases is surgical exploration of the mediastinum and histopathological examination of mediastinal lymph-node compartments (stations). Because the degree of anatomical resolution of mediastinal lymph nodes with PET is limited, we broadened the lymph-node categories in the classification of Mountain and Dresler[11] in order to compare the results of CT, PET, and histopathological analysis (Fig. 1). For the interpretation of the CT findings, the mediastinal lymph nodes were divided in two categories: those with a diameter of less than 1 cm in the shortest axis were considered normal in size and those with a diameter of 1 cm or more were considered to be enlarged.

Hot Spots outside the Mediastinum

Hot spots outside the mediastinum were described according to their anatomical locations and were related to data obtained by traditional staging methods, including the data obtained during the six-month follow-up in the case of lesions that had not been detected previously by traditional staging methods. If there was a clinical suspicion of distant metastases during the follow-up period, biopsies or imaging tests were performed. The results of PET were considered to be falsely positive if no metastases became apparent at a hot spot during follow-up.

Statistical Analysis

The study was designed to detect with a power of 0.85 and a two-sided α level of 0.05 a difference of 35 percent between the sensitivity of PET and that of CT (whose sensitivity was assumed to be 60 percent). In order to identify such a difference, the study required a minimum of 30 patients with mediastinal metastases. Assuming that mediastinal metastases are present in about 30 percent of patients with resectable non–small-cell lung cancer, a minimum of 100 patients had to be enrolled.

We determined the sensitivity, specificity, and diagnostic accuracy of each imaging method and of the combination of PET and CT.

The degree of agreement between observers was quantified with the kappa statistic. The two-sided sign test was used to compare the differences between the TNM class identified by PET and that identified by traditional methods of staging. Logistic-regression analysis was performed to evaluate the relative ability of PET and CT to identify metastatic cancer in mediastinal lymph nodes. A P value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was carried out with SPSS software.

RESULTS

Patients

Between September 1996 and December 1998, we evaluated 110 consecutive patients. Non–small-cell lung cancer was diagnosed in 102 patients: 58 had squamous-cell carcinoma, 28 had adenocarcinoma, 13 had large-cell carcinoma, 2 had adenosquamous carcinoma, and 1 had a neuroendocrine tumor. We excluded two patients with solitary metastases

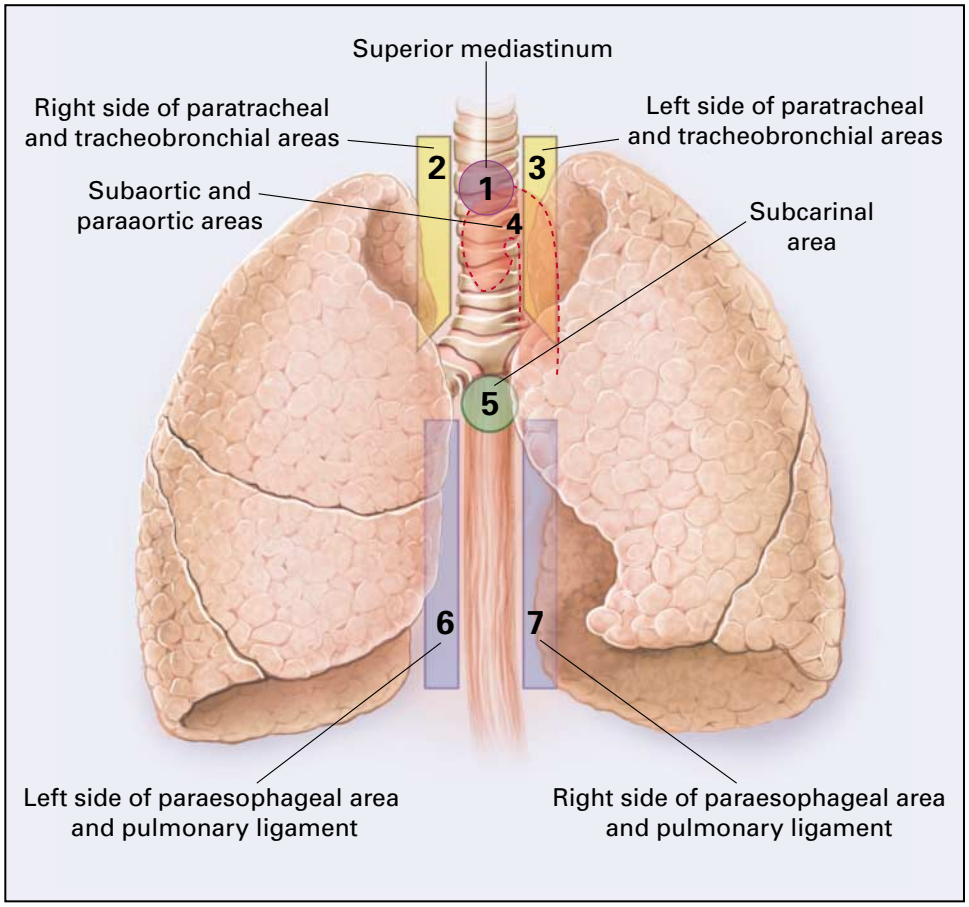

Figure 1. Mediastinal Lymph-Node Levels Used to Compare the Results of PET, CT, and Histopathological Analysis.
Level 1 included the superior mediastinum; level 2, the right side of the paratracheal and tracheobronchial areas; level 3, the left side of the paratracheal and tracheobronchial areas; level 4, the subaortic and paraaortic areas; level 5, the subcarinal area; level 6, the right side of the paraesophageal area and the pulmonary ligament; and level 7, the left side of the paraesophageal area and the pulmonary ligament.

from melanoma and breast cancer, respectively; one with tuberculosis; one with sarcoidosis; and four in whom mediastinal dissection was inadequate. The characteristics of the 102 patients who were evaluated are shown in Table 1.

Surgery

All patients underwent a cervical mediastinoscopy that explored lymph-node levels 1, 2, 3, and 5 (Fig. 1). In patients who underwent a right-sided thoracotomy, mediastinal lymph nodes at levels 1, 2, 5, and 6 were dissected, and in those who underwent a left-sided thoracotomy, lymph nodes at levels 1, 3, 4, 5, and 7 were dissected. Six patients with solitary parenchymal metastasis were considered to have resectable tumors. In three patients with solitary brain metastases, curative lobectomy was performed after the removal of the brain lesion. In two patients with two primary tumors in two lobes of the same lung, a curative pneumonectomy was performed. One patient with a non–small-cell lung cancer of stage T2N2M1 had a double tumor and microscopic tumor invasion of the subcarinal lymph nodes, all three of which were completely resected. In the group as a whole, 97 percent of the mediastinal lymph-node levels that could be reached were dissected (Table 1). At each level a median of 7 separate lymph nodes (range, 1 to 18) were dissected. Histopathological analysis showed that a total of 37 mediastinal lymph-node levels contained metastatic tumor.

Detection of Primary Tumor with PET

Every primary tumor was detected as an intense hot spot on PET scans (Fig. 2). In one patient with two primary tumors, the squamous-cell carcinoma appeared as a hot spot on PET, but surprisingly, the

TABLE 1. CHARACTERISTICS OF THE 102 PATIENTS WITH RESECTABLE NON–SMALL-CELL LUNG CANCER WHO COULD BE EVALUATED.

CHARACTERISTIC	VALUE
Sex (no. of patients)	
Male	88
Female	14
Median age (yr)	
Median	63
Range	25–77
Cervical mediastinoscopy (no. of patients)*	
Positive findings	15
Negative findings	87
Mediastinal exploration during thoracotomy (no. of patients)*	
Positive findings	17
Negative findings	70
Thoracotomy (no. of patients)	
Right-sided	48
Left-sided	39
No. of mediastinal lymph-node levels	
Surgically reachable	534
Surgically dissected	516
Pathological stage (no. of patients)†	
T1–4N0M0	47
T1–4N1M0	18
T1–4N2M0	28
T2N3M0	3
T1–4N1M1	3
T2N0M1	2
T2N2M1	1

*Positive and negative findings refer to the results of histopathological analysis.

†The tumor–node–metastasis (TNM) system of classification of the American Joint Committee on Cancer was used.[10]

adenocarcinoma was not detected, although it was clearly visualized on CT.

Detection of Mediastinal Metastases with PET

Mediastinal lymph-node metastases were correctly detected by PET in 29 of 32 patients with positive results on histopathological analysis (Table 2) and in 28 of the 37 mediastinal lymph-node levels that were positive for metastatic tumor on histopathological analysis. PET correctly identified 60 of 70 patients who did not have mediastinal lymph-node metastases on histopathological analysis (Table 2). Distinguishing between intrapulmonary involvement and mediastinal lymph-node involvement is an important part of the process of deciding whether thoracotomy should be performed. The sensitivity and specificity of PET for detecting mediastinal metastases were 91 percent (95 percent confidence interval, 81 to 100 percent) and 86 percent (95 percent confidence interval, 78 to 94 percent), respectively (Table 3). The overall negative predictive value of the method was 95 percent (95 percent confidence interval, 90 to 100 percent), and the positive predictive value was 74

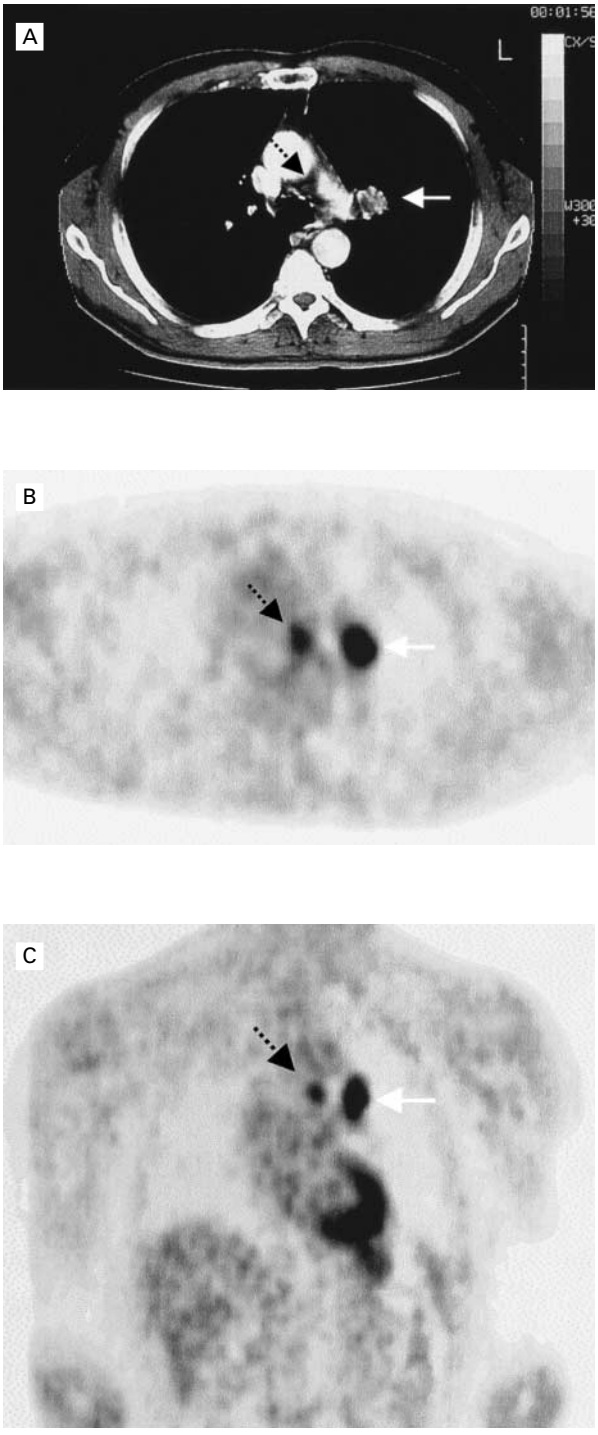

Figure 2. CT and PET Findings in a Centrally Located Adenocarcinoma of the Left Lung and a Small Pretracheal Lymph Node in a Patient with Non–Small-Cell Lung Cancer.

On the axial CT scan of the chest (Panel A), the primary tumor (white arrow) is adjacent to the pulmonary artery; the lymph node is indicated by the dotted arrow. On the axial PET scan (Panel B) and coronal PET scan (Panel C), the primary tumor (white arrows) and lymph node (dotted arrows) show increased uptake of ^{18}F-fluorodeoxyglucose. Physiologic uptake of ^{18}F-fluorodeoxyglucose by the myocardium is also apparent.

TABLE 2. RESULTS OF CT, PET, AND HISTOPATHOLOGICAL ANALYSES OF MEDIASTINAL LYMPH NODES IN PATIENTS WITH RESECTABLE NON–SMALL-CELL LUNG CANCER.

FINDINGS ON HISTOPATHOLOGICAL ANALYSIS*	FINDINGS ON PET	FINDINGS ON CT		TOTAL NO. OF PATIENTS
		NEGATIVE	POSITIVE	
Negative	Negative	43	17	60
Negative	Positive	3	7	10
Total		46	24	70
Positive	Negative	1	2	3
Positive	Positive	7	22	29
Total		8	24	32

*Lymph-node specimens were obtained by biopsy during cervical mediastinoscopy or dissected as part of mediastinal exploration during thoracotomy.

TABLE 3. SENSITIVITY, SPECIFICITY, AND ACCURACY OF CT, PET, AND BOTH CT AND PET AS COMPARED WITH HISTOPATHOLOGICAL ANALYSIS FOR THE MEDIASTINAL EVALUATION OF PATIENTS WITH RESECTABLE NON–SMALL-CELL LUNG CANCER.

METHOD*	SENSITIVITY	SPECIFICITY	ACCURACY
	percent (95% confidence interval)		
CT	75 (60–90)	66 (55–77)	69 (60–78)
PET	91 (81–100)	86 (78–94)	87 (80–94)
PET and CT†	94 (86–100)	86 (78–94)	88 (82–94)

*The results of each method were compared with the results of histopathological analysis.

†For each pair of tests, the results of at least one imaging technique were positive.

percent (95 percent confidence interval, 60 to 88 percent). Because of the presence of reactive hyperplasia in the mediastinal lymph nodes of seven patients and of silicoanthracosis in three, PET produced a false positive result. False negative results were due to microscopic-tumor residue in two patients and to the inability of the method to distinguish between paramediastinal primary tumor and mediastinal lymph nodes in one patient. The degree of interobserver agreement (kappa value) in detecting mediastinal hot spots was 0.87 (95 percent confidence interval, 0.64 to 1.0).

Detection of Distant Metastases with PET

In 20 of 102 patients, 29 hot spots were detected outside the mediastinum (Fig. 3). Three malignant satellite nodules in the resected lobe were confirmed to be present during histologic examination, and 17 of the 29 hot spots were diagnosed as metastases during the follow-up period — 3 by means of biopsy, 5 on the basis of the detection of new, growing lesions on ultrasonography, 5 by means of CT, and 4 on the basis of a finding of lytic lesions on radiographic imaging. Nine hot spots — four in the colon, two in the lung, and one each in the liver, adrenal glands, and rib — were considered to be false positive results, since no metastases were identified in these areas during the follow-up period.

PET correctly identified distant metastases in 11 of 102 patients (11 percent) in whom the usual methods of staging had found none. In three other patients, intrapulmonary metastases had been detected by CT. In three patients without hot spots, distant metastases developed during follow-up. No distant metastases were diagnosed during follow-up in 79 patients without hot spots on PET. The sensitivity and specificity of PET for detecting distant metastases alone were 82 percent (95 percent confidence interval, 64 to 100 percent) and 93 percent (95 percent confidence interval, 88 to 98 percent), respectively. The degree of interobserver agreement was 0.98 (95 percent confidence interval, 0.73 to 1.0).

CT of the Chest

In 20 of the 37 lymph-node levels that were positive for metastatic tumor on histopathological analysis, CT revealed enlarged mediastinal lymph nodes. CT correctly identified 46 of 70 patients who did not have mediastinal metastases on histopathological analysis and 24 of 32 patients who did have mediastinal metastases (Table 2). In eight patients with mediastinal lymph-node metastases, the size of the lymph nodes was normal. The sensitivity of CT was 75 percent (95 percent confidence interval, 60 to 90 percent), and the specificity was 66 percent (95 percent confidence interval, 55 to 77 percent). An example of a mediastinal metastasis that was identified as a hot spot on PET but was deemed normal on CT is shown in Figure 4.

Overall Prognostic Value of PET

The overall sensitivity and specificity of PET, as compared with histopathological analysis, in detecting mediastinal and distant metastatic disease were 95 percent (95 percent confidence interval, 88 to 100 percent) and 83 percent (95 percent confidence interval, 74 to 92 percent), respectively. Logistic-regression analysis revealed that the results of both PET and CT were significantly correlated with the results of histopathological analysis. When adjusted for each other, however, the correlation remained significant only for PET ($P<0.001$). The use of PET for clinical staging resulted in a different stage from the one arrived at by the usual methods in 62 of 102 patients.

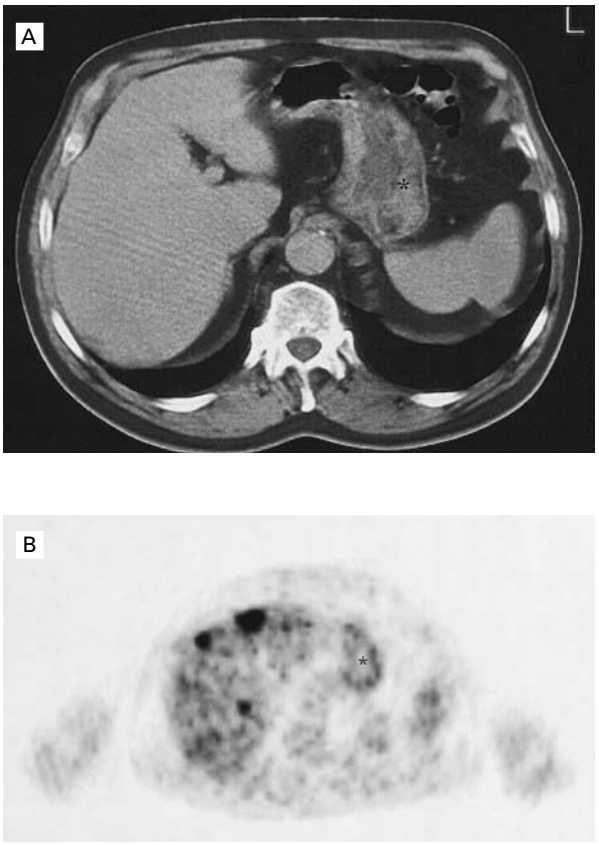

Figure 3. Preoperative Axial CT and PET Findings in a Patient with Non–Small-Cell Lung Cancer.

The preoperative CT scan revealed no metastases in the liver (Panel A), whereas the PET scan showed three hot spots in the liver (Panel B). Liver metastases were confirmed during follow-up. In Panel B, the asterisk indicates diffuse uptake of ^{18}F-fluorodeoxyglucose in the stomach wall as a result of gastritis.

In 20 patients the stage determined by PET was lower, and in 42 patients it was higher ($P<0.01$ by the two-sided sign test).

DISCUSSION

The ability of PET to identify tumors depends primarily on the degree of uptake of ^{18}F-fluorodeoxyglucose by malignant cells, the size of the tumor, and the presence or absence of inflammation. Non–small-cell lung-cancer cells avidly incorporate ^{18}F-fluorodeoxyglucose because they have an increased rate of glycolysis and overexpress the glucose transporter.[15] At presentation, most non–small-cell lung cancers are large enough to have hot spots on PET scans. Inflammation from an obstructing endobronchial tumor or other inflammatory processes cause most of the false positive hot spots on PET scans. Previous studies have found that PET has good sensitivity and

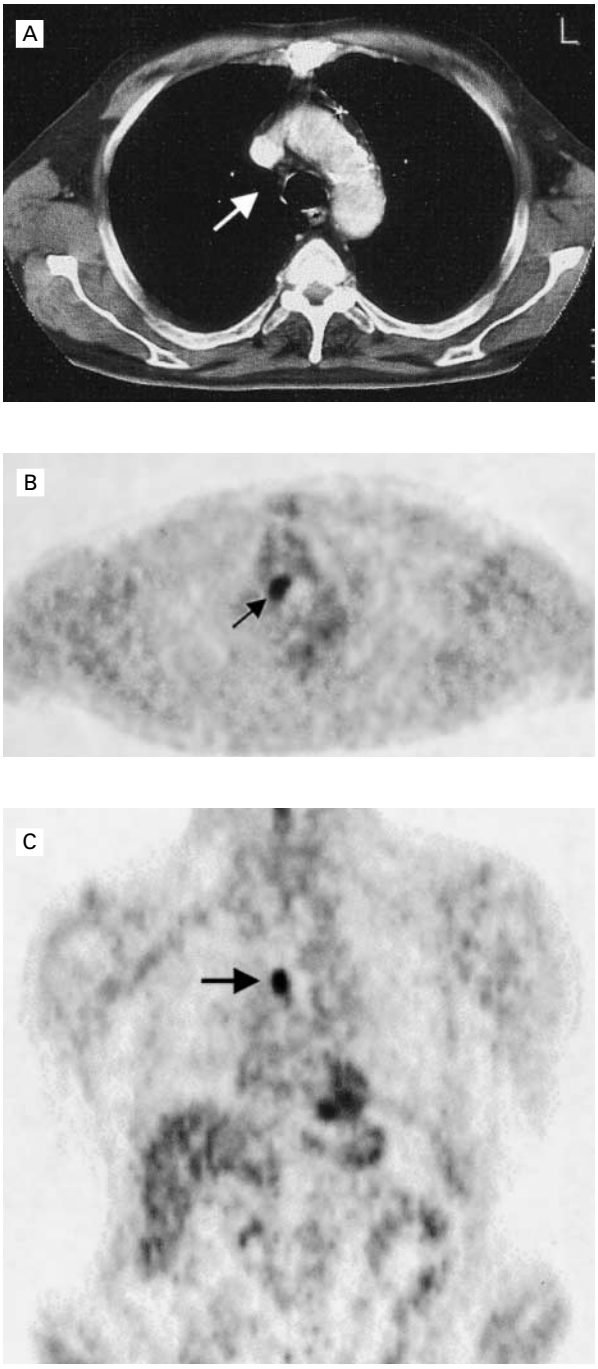

Figure 4. CT and PET Findings in a Patient with Squamous-Cell Carcinoma of the Right Lung.

No abnormal mediastinal lymph nodes were observed at level 2 on the CT scan (Panel A). On the corresponding axial PET scan (Panel B) and coronal PET scan (Panel C), the uptake of ^{18}F-fluorodeoxyglucose was increased (arrows). The arrow in Panel A indicates the area of increased uptake in Panels B and C.

specificity for detecting mediastinal lymph-node metastases, but some of these investigations did not report to what extent surgical exploration was used to confirm the presence of such metastases.[5,6,16] The sensitivity and specificity of this method can be misleadingly high if a biopsy of normal-sized lymph nodes with minimal tumor is not performed. To relate PET data to histopathological data, both normal-appearing and abnormal-appearing lymph nodes must undergo biopsy or be removed for further examination. In our study, 97 percent of the mediastinal lymph-node levels that could be reached surgically were dissected and underwent histopathological analysis.

A disadvantage of PET is its limited anatomical resolution, which makes assessment of the extent of the primary tumor, especially if it invades the mediastinum, unreliable. For the same reason, mediastinal hot spots can be related only to lymph-node levels and not to individual lymph nodes. We defined these levels during the preliminary part of the study to facilitate the interpretation of distinct hot spots in the mediastinum.

Another problem with PET is that ^{18}F-fluorodeoxyglucose accumulates as part of the physiologic process in the brain and urinary tract, which makes an evaluation of metastases at these sites difficult. A qualitative analysis of PET images can serve only to rule out the presence of such metastases and not to identify them.[7,17] This point brings the usefulness of transmission scanning for this purpose into question, although the results of mediastinal and hepatic scanning are slightly improved after correction for attenuation of the ^{18}F-fluorodeoxyglucose signal. The use of CT together with PET may help to pinpoint the anatomical location of the hot spot, especially in the case of intrapulmonary lymph nodes, which are located close to the mediastinum and thus can be mistaken for mediastinal lymph nodes.[18] However, in one study, computerized fusion of the two types of images seemed to be only marginally more beneficial than simple visual correlation of the PET scan and CT scan in terms of pinpointing metastases in thoracic lymph nodes.[19] We also found that combining CT with PET did not significantly improve sensitivity and specificity.

The high negative predictive value of PET for mediastinal lymph-node metastases can be used to advantage in the approach to patients with non–small-cell lung cancer, because invasive procedures are probably not necessary in a patient with negative findings on PET in the mediastinum. However, our finding of a positive predictive value of 74 percent means that patients in whom a mediastinal hot spot is found on PET will need to undergo a cervical mediastinoscopy as part of the workup for non–small-cell lung cancer. The positive predictive value will be lower in patients with inflammatory changes.[20,21]

Frequent sites of distant metastasis in patients with non–small-cell lung cancer are the liver, adrenal glands, bone, and brain. Whole-body PET can replace other types of imaging for all these sites except the brain, where the degree of uptake of ^{18}F-fluorodeoxyglucose lacks specificity. The use of PET to identify distant metastases in patients with non–small-cell lung cancer has not been extensively studied, but the method may offer better results for bone metastases than bone scanning.[8] If we had not also performed invasive procedures in our study, 17 percent of patients would have been denied potentially curative surgery because of false positive mediastinal or distant hot spots or both. For this reason, a positive PET result requires an evaluation involving mediastinoscopy and, if indicated for distant lesions, additional procedures.

Our study confirms that, as compared with traditional staging methods, PET can result in a more accurate classification of the stage of disease in patients with resectable non–small-cell lung cancer. The increased accuracy may improve survival, but this outcome was not the primary end point of our study. Therefore, a randomized study is necessary to determine whether a diagnostic strategy that includes PET can improve survival. However, some small studies have suggested that the use of standardized uptake values for the primary tumor has independent prognostic value.[22,23]

Concurrent detection of mediastinal and distant metastases by ^{18}F-fluorodeoxyglucose PET will decrease the number of tests and invasive procedures required in the evaluation of patients with non–small-cell lung cancer. Implementing PET at the start of the staging process may improve the efficiency of the workup, but at this time the procedure is not cost effective, given the limited availability of dedicated PET cameras.

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