Stage T1 Non–Small Cell Lung Cancer: Preoperative Mediastinal Nodal Staging with Integrated FDG PET/CT—A Prospective Study[1]

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Purpose: To prospectively evaluate the sensitivity and specificity of integrated fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) and computed tomography (CT) (PET/CT) for the preoperative diagnosis of mediastinal nodal metastasis in stage T1 non–small cell lung cancer (NSCLC), with surgical and histologic results as reference standards.

Materials and Methods: Institutional review board approval and informed consent were obtained. From June 2003 to February 2005, 150 patients (89 men and 61 women; mean age, 59 years) with stage T1 NSCLC at stand-alone CT underwent integrated PET/CT and surgical staging. Two observers (one radiologist and one nuclear medicine physician) evaluated prospectively and in consensus the mediastinal nodes by analyzing both PET (functional) and CT (anatomic) images. Nodal stages were determined by using the American Joint Committee on Cancer staging system and surgical and histologic findings as the reference standard. Statistical evaluation of malignant lymph nodes was performed on per-nodal-station and per-person bases.

Results: A total of 568 mediastinal nodal stations were evaluated. Nodes were positive for malignancy in 34 (23%) of 150 patients and 55 (10%) of 568 nodal stations. For depiction of malignant nodes, the respective sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of integrated PET/CT were 42% (23 of 55), 100% (513 of 513), 100% (23 of 23), 94% (513 of 545), and 94% (536 of 568) on per-nodal-station basis and 47% (16 of 34), 100% (116 of 116), 100% (16 of 16), 87% (116 of 134), and 88% (132 of 150) on a per-patient basis.

Conclusion: Integrated FDG PET/CT provides high specificity and positive predictive value of mediastinal nodal staging in stage T1 NSCLC, although the sensitivity is low.

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Patients with stage T1 non–small cell lung cancer (NSCLC) (lung cancer <3 cm in diameter) without nodal or distant metastasis, designated stage IA (T1N0M0) according to the TNM staging system, have a 5-year postoperative survival rate of about 70% (1,2). Because studies suggest a low prevalence of mediastinal nodal metastases and because mediastinoscopy is an invasive procedure, there has been some debate among thoracic surgeons about the merits of performing routine mediastinoscopy in patients with stage T1 NSCLC. However, authors of several recent studies (3–5) have reported relatively high frequencies of mediastinal lymph node metastases in stage T1 NSCLC, ranging from 16% to 21% by means of complete nodal sampling at mediastinoscopy or thoracotomy. Therefore, a precise knowledge of mediastinal nodal metastasis in stage T1 NSCLC provides guidance concerning optimal staging procedures (mediastinoscopy) and treatment (surgery vs neoadjuvant chemotherapy and radiation with or without subsequent surgery).

Although computed tomography (CT) has been widely used for preoperative evaluation of tumor size and adjacent structure invasion, findings of a number of studies (5–9) have shown that CT is limited in its ability to help stage lung cancer because of its shortcomings with respect to lymph node staging. Overall, CT has a sensitivity of 41%–63%, a specificity of 43%–57%, and an accuracy of 39%–59% for the detection of mediastinal nodal metastasis (6,7,9,10). Moreover, in stage T1 lung cancer, CT has a sensitivity of only 27%–41% (5,10). These low values are probably related to the definition of positive nodes according to size criteria alone: low sensitivity values due to the failure of CT to depict metastases in small-sized lymph nodes or low specificity values due to enlarged hyperplastic nodes that do not contain metastases (5,6,11).

Positron emission tomography (PET) with fluorine 18 fluorodeoxyglucose (FDG) has been reported to improve nodal metastasis identification. FDG PET images may be more sensitive because alterations in tissue metabolism generally precede anatomic changes (12). Integrated PET/CT, by combining morphologic CT data and functional PET data, generally provides satisfactory spatial resolution and anatomic and metabolic information. Moreover, integrated PET/CT scanners have produced promising initial oncologic imaging results (13,14).

However, the resolution of PET may still be insufficient to depict lymph node metastases in small-sized nodes, and nodal metastasis to lymph nodes of 5 mm or less in diameter may be missed (13,14). Therefore, negative PET/CT results may not obviate mediastinoscopy for mediastinal staging. Thus, the purpose of our study was to prospectively evaluate the sensitivity and specificity of integrated FDG PET/CT for the preoperative diagnosis of mediastinal nodal metastasis in stage T1 NSCLC by using surgical and histologic results as reference standards.

Advances in Knowledge

- On a per-patient basis, integrated PET/CT had a 100% positive predictive value and an 87% negative predictive value but a low sensitivity (47%) for the detection of mediastinal nodal metastasis in T1 non–small cell lung cancer.
- Negative results at integrated PET/CT do not obviate mediastinoscopy for mediastinal nodal staging.

Materials and Methods

Our institutional review board approved our study, and written informed consent was obtained from all patients for this prospective study.

Patient Population

A total of 186 patients with histopathologically proved NSCLC of less than 3 cm in the longest diameter on CT scans were enrolled. All consecutive patients referred for surgery between June 2003 and February 2005 were included, and all underwent conventional lung cancer staging on the basis of clinical information, stand-alone chest CT with intravenous injection of 100 mL of iopamidol (Iopamiron 300; Bracco, Milan, Italy), and an integrated whole-body PET/CT study. Nine patients were excluded because conventional staging studies or integrated whole-body PET/CT suggested extrathoracic metastasis; eight, because they received chemotherapy ($n = 1$) or chemotherapy and radiation ($n = 7$) before surgical staging at another hospital; and 19, because they had primary lung cancer invading the visceral pleura or more proximally into the lobar bronchus than expected (stage T2 lung cancer) according to histopathologic findings.

Thus, 150 patients (89 men and 61 women; mean age, 59 years; range, 33–81 years) were included. Of the 150 patients, 38 belonged to the patient population of our previous report (14) and the remaining 112 patients were new. All patients underwent surgical staging. The mean interval between the initial histologic diagnosis of NSCLC and integrated PET/CT was 4 days (range, 0–23 days; median, 3 days), whereas that between integrated PET/CT and surgical staging was 10 days (range, 1–96 days; median, 6 days). Nodal stages were classified according to the American Joint Committee on Cancer staging systems (15). Histopathologic results served as the reference standard. Forty-nine (33%) of 150 patients had a medical history of pulmonary tuberculosis as determined at clinical or imaging studies.

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Abbreviations:
FDG = fluorine 18 fluorodeoxyglucose
NSCLC = non–small cell lung cancer
SUV = standardized uptake value

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Integrated PET/CT Acquisition

All patients fasted for at least 6 hours before the PET/CT examination, although oral hydration with glucose-free water was allowed. After a normal blood glucose level in the peripheral blood was ensured, patients received an intravenous injection of 370 MBq (10 mCi) of FDG and then rested for approximately 45 minutes before undergoing imaging. Image acquisition was performed with an integrated PET/CT device (Discovery LS, GE Medical Systems) that consisted of a PET scanner (Advance NXi; GE Medical Systems) and an eight-section CT scanner (Light Speed Plus; GE Medical Systems). The axes of both systems were mechanically aligned so that by shifting the examination table 68 cm, the patient was moved from the CT gantry into the PET gantry. The resulting PET and CT images were coregistered by using computer hardware.

CT was performed from the head to the pelvic floor by using a standardized protocol that involved 140 kV, 80 mA, a tube-rotation time of 0.5 seconds per rotation, a pitch of 6, and a section thickness of 5.0 mm, which matched the PET image section thickness. Patients were allowed normal shallow respiration during the acquisition of CT scans. No contrast material was administered. Immediately after CT, PET was performed in an identical transverse field of view. The acquisition time for PET was 5 minutes per table position. CT data were resized from a 512×512 matrix to a 128×128 matrix to match the PET data to allow image fusion, and CT transmission maps were generated. PET image data sets were reconstructed iteratively by using the ordered subsets expectation maximization algorithm with segmented attenuation correction (two iterations, 28 subsets) and the CT data. Coregistered images were displayed by using software (eNTEGRA; GE Medical Systems), which allowed image fusion and analysis.

Integrated PET/CT Image Analysis

One chest radiologist (K.S.L., with 16 years of CT interpretation experience) and one of two nuclear medicine physicians (B.T.K. and J.Y.C., 11 and 5 years of experience, respectively, and each with 2 years of experience in integrated PET/CT analysis), who were blinded to clinical, stand-alone CT, and pathologic results, prospectively evaluated the integrated PET/CT data sets. Decisions about findings were reached in consensus. Nodal stations were evaluated and allocated to nine groups, according to the lymph node map definition for lung cancer staging proposed by Mountain and Dresler (1): group 1, highest mediastinal (1R, right; 1L, left); group 2, upper paratracheal (2R, right; 2L, left); group 3, prevascular and retrotracheal; group 4, lower paratracheal (4R, right; 4L, left); group 5, subaortic (aortopulmonary window); group 6, paraaortic (ascending aorta or phrenic); group 7, subcarinal; group 8, paraesophageal; and group 9, pulmonary ligament (9R, right; 9L, left). Mediastinal nodes with an increased glucose uptake and a distinct margin were considered positive. Increased uptake was defined qualitatively as a level greater than that of the surrounding mediastinal tissue and quantitatively as a maximum standardized uptake value (SUV), adjusted for body weight, of more than 3.5.

Prior receiver operating characteristic analysis at different SUV threshold cutoffs showed that an SUV of 3.5 was optimum for differentiating benign and malignant tissues with our machines (14,16). Mediastinal nodes were divided into the following four categories according to the integrated PET/CT results: positive uptake with neither calcification nor high attenuation, positive uptake with calcification or high attenuation, negative uptake with calcification or high attenuation, and negative uptake with neither calcification nor high attenuation. Calcification was considered present when it was nodular, laminated, or diffuse and attenuation was 200 HU or greater. A high-attenuation node was defined as one that appeared to have attenuation higher than that of mediastinal vascular structures and 70 HU or greater according to receiver operating characteristic measurement. Even if glucose uptake was high (higher than background activity and more than 3.5 in maximum SUV), calcified lymph nodes or lymph nodes with a higher attenuation than the surrounding great vessels on the CT images of integrated PET/CT were regarded as benign (14).

Surgical and Histopathologic Analyses

Surgical staging included mediastinoscopy alone ($n = 15$), mediastinoscopy and thoracotomy ($n = 101$), or thoracotomy alone ($n = 34$). Surgical staging was performed by one of two experienced thoracic surgeons (Y.M.S. and J.K., 17 and 12 years of experience, respectively). In 15 patients, only mediastinoscopic nodal staging results were available because curative resection was deferred, owing to the presence of positive nodes, in favor of neoadjuvant concurrent chemotherapy and radiation. Tumor resection and extensive mediastinal lymph node dissection with thoracotomy were performed in 135 patients. Thoracotomy was performed after the results of preoperative imaging examinations (ie, integrated PET/CT) were considered. During mediastinoscopy, American Thoracic Society lymph node map areas of 2R, 4R, 2L, 4L, and 7 were routinely sampled; during thoracotomy, according to our routine surgical protocol, surgeons dissected all visible and palpable lymph nodes accessible in the mediastinum irrespective of their sizes. Specifically, all encountered lymph nodes were removed from the American Thoracic Society lymph node map areas of 10R, 9, 8, 7, 4R, 3, and 2R in tumors of the right lung and from areas 10L, 9, 8, 7, 6, 5, and 4L of the left lung. When necessary, especially when imaging results suggested possible nodal metastasis in other nodal stations than routine lymph node dissection, group 1 (highest mediastinal) or 2L (tumors located in the left lung) nodes were also evaluated during mediastinoscopy or thoracotomy.

Patients in whom the primary tumor was limited to a lobe ($n = 124$) underwent lobectomy; those with hilar lymph nodes of extracapsular invasion underwent bilobectomy ($n = 6$), sleeve lobectomy ($n = 3$), or pneumonectomy ($n = 2$). A lung pathologist with 10 years of experience described the tumors (ie, histopathologic class, size, involvement of surrounding organs, necrosis, distance from the resection margin), if thoracotomy was performed, and lymph nodes

(location and number). Surgeons labeled dissected lymph nodes by numbering the nodes according to the lymph node map definition for lung cancer staging proposed by Mountain and Dresler (1). Subsequently, the pathologist evaluated the nodes as numbered in the surgical field and recorded the presence or absence of tumor in the nodes. Specimens were stained with hematoxylin-eosin and were examined with light microscopy. The pathologic stage was recorded for each patient; a total of 568 nodal groups from 150 patients were dissected.

Retrospective CT Evaluation

Two chest radiologists (K.S.L. and S.S.S., 16 and 2 years of CT interpretation experience, respectively), who were also blinded to stand-alone CT and pathologic results, evaluated the CT component of the integrated PET/CT after completion of surgical staging. Decisions about findings were reached in consensus, and the short-axis diameters of detected lymph nodes in the mediastinum were recorded. Nodal stations were evaluated by allocating them to nine groups according to the lymph node map definition for lung cancer staging used previously for the interpretation of integrated PET/CT images. The presence of benign calcification (nodular, laminated, or diffuse) or diffuse high attenuation (>70 HU) within nodes was also recorded for all detected nodes.

Statistical Analysis

The presence of mediastinal nodal metastasis in terms of histopathologic subtypes of lung cancer was recorded on a per-person basis and was compared between adenocarcinoma and other cell types by using the two-tailed Fisher exact test. Detection rates of nodal metastasis at integrated PET/CT on a per-nodal-station basis were compared according to histopathologic subtypes, also by using the Fisher exact test. Sensitivity, specificity, positive and negative predictive values, and accuracy of detection rates of malignant lymph nodes were assessed on a per-patient basis and on a per-nodal-station (nine stations) basis.

To determine retrospectively the smallest lymph node diameter at CT that demonstrated a true-positive uptake at PET and the largest node diameter at CT that demonstrated a true-negative uptake at PET, we stratified nodes according to size into five groups (absent, <5 mm, 5 to <8 mm, 8 to <10 mm, and ≥10 mm). We then evaluated the proportions of nodes according to size that were true-positive or true-negative at histopathologic examination.

We also retrospectively evaluated how accurately nodes with benign calcification or diffuse high attenuation (>70 HU) at CT and positive uptake at PET represented benignancy as determined histopathologically. In other words, by identifying calcification or high attenuation at CT (although nodes demonstrated high uptake at PET), we evaluated how well benign nodes with these characteristics at integrated PET/CT were classified as benign.

Results

Histologic Analysis

Histologic analysis revealed adenocarcinoma in 112 patients, squamous cell

Table 1

Detection of Lymph Node Metastasis at PET/CT

Parameter	Lymph Node Group No.									Total
	1	2	3	4	5	6	7	8	9	
No. of false-negative findings	0	6	2	11	4	1	6	0	2	32
No. of true-positive findings at PET/CT	0	3	1	9	1	0	9	0	0	23
No. of true-positive nodal groups/no. of nodal groups evaluated	0/2	9/70	3/22	20/188	5/47	1/6	15/141	0/8	2/84	55/568

Note.—Group 1 = highest mediastinal, group 2 = upper paratracheal, group 3 = prevascular and retrotracheal, group 4 = lower paratracheal, group 5 = subaortic (aortopulmonary window), group 6 = paraaortic (ascending aorta or phrenic), group 7 = subcarinal, group 8 = paraesophageal, group 9 = pulmonary ligament.

Table 2

Mediastinal Nodal Staging Results at PET/CT of Different Histopathologic Subtypes of Lung Cancer

Statistic	Squamous Cell Carcinoma (n = 25)		Adenocarcinoma (n = 112)		Other* (n = 13)	
	Per Node	Per Patient	Per Node	Per Patient	Per Node	Per Patient
Sensitivity	2/4 (50)	2/4 (50)	21/51 (41)	14/30 (47)	0	0
Specificity	78/78 (100)	21/21 (100)	390/390 (100)	82/82 (100)	45/45 (100)	13/13 (100)
Positive predictive value	2/2 (100)	2/2 (100)	21/21 (100)	14/14 (100)	0	0
Negative predictive value	78/80 (98)	21/23 (91)	390/420 (93)	82/98 (84)	45/45 (100)	13/13 (100)
Accuracy	80/82 (98)	23/25 (92)	411/441 (94)	96/112 (86)	45/45 (100)	13/13 (100)

Note.—Data in parentheses are percentages.

* Includes six bronchioloalveolar carcinomas, four large-cell neuroendocrine cancers, two atypical carcinoids, and one pleomorphic carcinoma.

carcinoma in 25, bronchioloalveolar carcinoma in six, large cell neuroendocrine cancer in four, atypical carcinoid in two, and pleomorphic carcinoma in one.

Nodal FDG Uptake

A total of 568 nodal groups were sampled (mean number of nodal stations sampled per patient, 3.8). There were two highest paratracheal (nodal station 1), 70 upper paratracheal (station 2), 188 lower paratracheal (station 4), 22 prevascular and retrotracheal (station 3), 47 subaortic (station 5, aortopulmonary), six paraaortic (station 6), 141 subcarinal (station 7), eight paraesophageal (station 8), and 84 pulmonary ligament (station 9) nodes according to pathologic examinations. Of these, 55 nodal groups (10%) proved to be positive for malignancy in 34 (23%) of 150 patients. Among the positive nodes, nine were upper paratracheal; three, prevascular and retrotracheal; 20, lower paratracheal; five, subaortic; one, paraaortic; 15, subcarinal; and two, pulmonary ligament nodes (Tables 1, 2).

Thirty (27%) of 112 patients with adenocarcinoma, four (16%) of 25 patients with squamous cell carcinoma, and none (0%) of 13 patients with other cell type carcinomas had mediastinal nodal metastasis (N2 disease). Patients with adenocarcinoma showed significantly higher mediastinal nodal metastatic rates than did those with other cell types, including squamous cell and other cell type carcinomas ($P = .044$, two-tailed Fischer exact test). Twenty-one (41%) of 51 metastatic nodes in adenocarcinoma showed positive FDG uptake, whereas two (50%) of four metastatic nodes in squamous cell carcinoma showed FDG uptake. There was no significant difference in positive FDG uptake rates for true-positive nodes between adenocarcinomas and squamous cell carcinomas ($P > .99$) (Table 2).

Figure 1

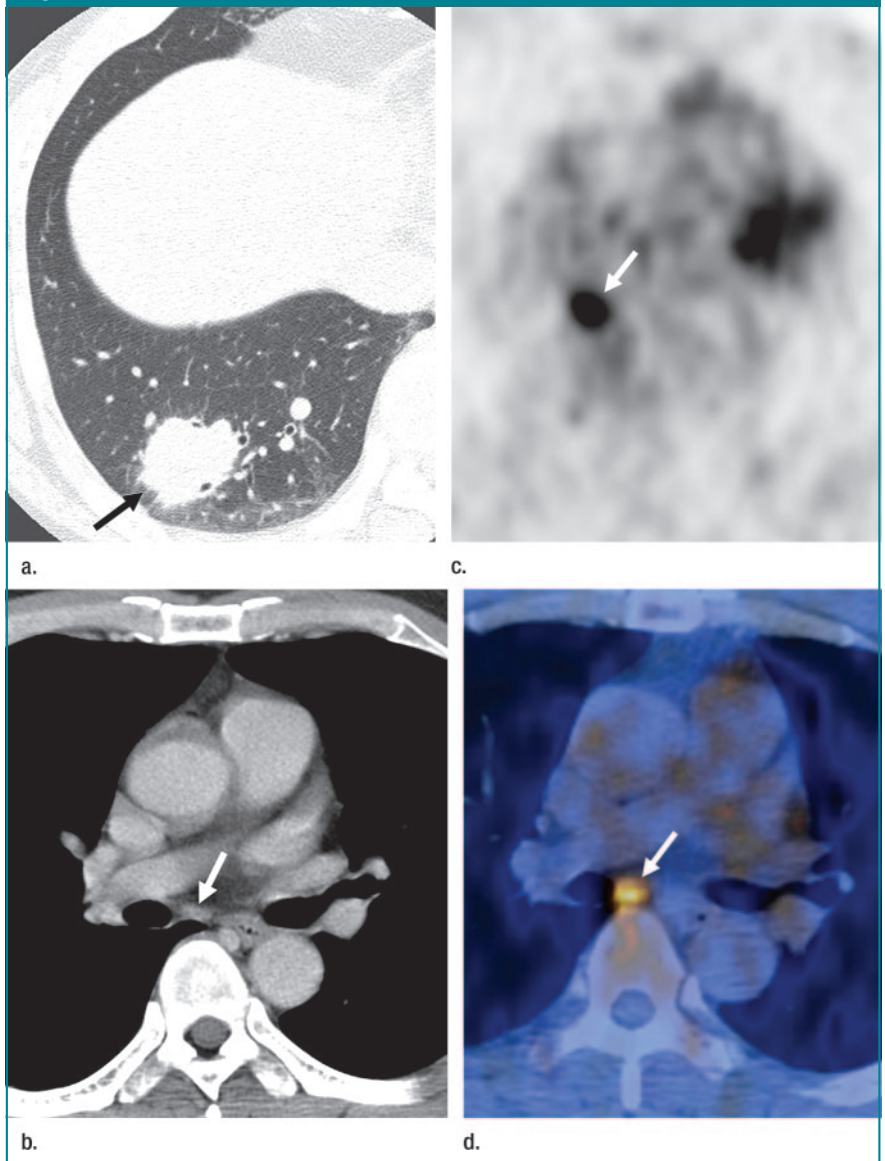

Figure 1: True-positive mediastinal lymph node metastasis at integrated PET/CT in 46-year-old man with adenocarcinoma of the lung. **(a)** Lung window view of transverse CT scan (2.5-mm collimation, 170 mA) at level of liver dome shows 28-mm nodule (arrow) with lobulated margin in right lower lobe. **(b)** Mediastinal window view of transverse unenhanced CT scan (5.0-mm collimation, 80 mA) at level of right bronchus intermedius shows 3.8-mm (short-axis diameter) lymph node (arrow) in subcarinal area (nodal station 7). Transverse **(c)** PET and **(d)** integrated PET/CT scans at level similar to **b** demonstrate node with markedly increased FDG uptake (maximum SUV, 7.9) (arrow) strongly suggesting malignant node, which proved to contain metastatic adenocarcinoma cells.

Statistical Parameters

For depiction of malignant nodes, the respective overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of integrated PET/CT were 47% (16 of 34 patients with positive nodes), 100% (116 of 116 patients with negative nodes), 100% (16 of 16), 87% (116 of 134), and 88% (132 of 150) on a per-patient basis and 42% (23 of 55), 100% (513 of 513), 100% (23 of 23), 94% (513 of 545), and 94% (536 of 568) on a per-nodal-station basis. Thirty-two false-negative interpretations were rendered at PET/CT for 17 paratracheal (nodal stations 2 and 4), six subcarinal, four subaortic, two pulmonary ligament, two prevascular,

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Figure 2

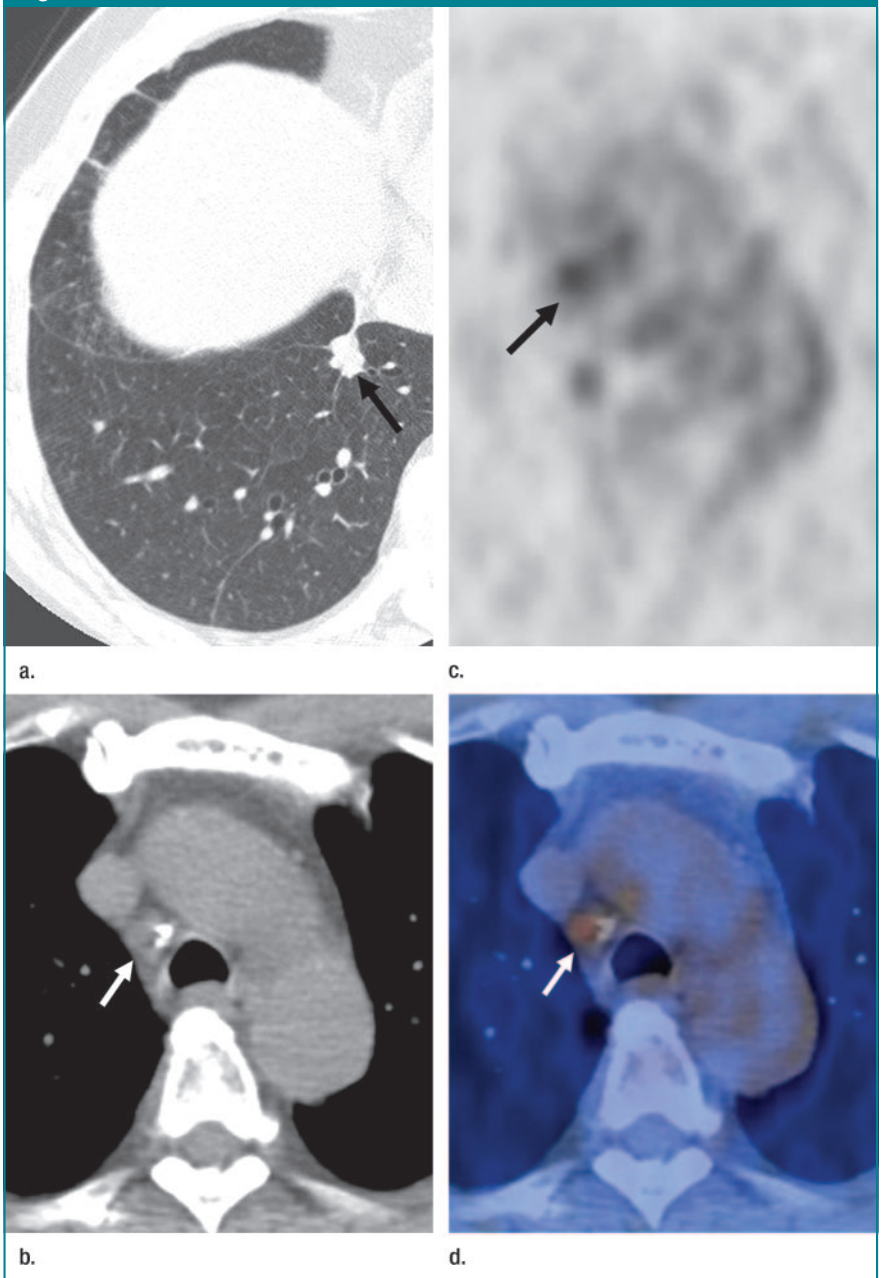

Figure 2: True-negative mediastinal lymph node metastasis at integrated PET/CT in 67-year-old man with adenocarcinoma of the lung. **(a)** Lung window view of transverse CT scan (2.5-mm collimation, 170 mA) at level of liver dome shows 10-mm nodule (arrow) with lobulated margin in right lower lobe. **(b)** Mediastinal window view of transverse unenhanced CT scan (5.0-mm collimation, 80 mA) at level of aortic arch shows 13-mm (short-axis diameter) lymph node (arrow) in right lower paratracheal area (nodal station 4R) with peripheral calcification. Transverse **(c)** PET and **(d)** integrated PET/CT scans at level similar to **b** demonstrate right lower paratracheal node showing increased FDG uptake (maximum SUV, 3.8) (arrow). Because there was calcification in this node, it was interpreted as benign and proved to be benign at histopathologic examination.

and one paraaortic nodal stations. No false-positive interpretation was rendered during nodal station evaluations (Table 1).

Nodal Size at CT

The smallest node at CT that showed a true-positive uptake at integrated PET/CT was 3.8 mm in short-axis diameter, and the largest node at CT that showed a true-negative uptake at integrated PET/CT was 19 mm in diameter (Fig 1). Fifty-two (95%) of 55 pathologically proved malignant nodal stations were less than 10 mm in short-axis diameter or were unidentifiable at CT (Tables 2, 3). Twenty (87%) of 23 true-positive nodal stations at PET/CT were less than 10 mm in short-axis diameter (Table 2), and six (1%) of 512 true-negative nodal stations at PET/CT were 10 mm or greater in diameter, regardless of the presence of calcification or an attenuation greater than 70 HU (Fig 2). All 32 false-negative nodes at PET/CT were less than 10 mm in diameter (Tables 3, 4; Fig 3).

Nodal High Attenuation or Calcification at CT

Forty-six (94%) of 49 nodes with either calcification (n = 37, 35 nodular and two laminated) or high attenuation (>70 HU) (n = 12) and high uptake at PET (up to maximum SUV, 11.7) appeared to be true-negative at pathologic examination (Fig 2), whereas the remaining three (6%) turned out to be false-negative.

Discussion

In our study, mediastinal nodes were positive for malignancy in 34 (23%) of 150 patients and 55 (10%) of 568 nodal stations in stage T1 NSCLC. This frequency of mediastinal nodal metastasis on a per-person basis is slightly higher than the previous reports of 16%–21% (3–5).

CT is limited in its ability to help stage mediastinal lymph node involvement because it allows mediastinal lymph node metastasis assessment mainly on the basis of nodal size. This is supported by reports that false-negative

Table 3

Size and Internal Characteristics of Lymph Nodes at CT for True-Positive and False-Positive Interpretations at PET/CT

Interpretation	Unidentified	Node < 5 mm		5 mm ≤ Node < 8 mm		8 mm ≤ Node < 10 mm		Node ≥ 10 mm	
		No	Yes	No	Yes	No	Yes	No	Yes
True-positive (n = 23)	0	1	0	16	0	3	0	3	0
False-positive (n = 0)	0	0	0	0	0	0	0	0	0
Total (n = 23)	0	1	0	16	0	3	0	3	0

Note.—Unidentified = no visible nodes in corresponding nodal station at CT, No = neither benign calcification nor internal diffuse high attenuation on nodes greater than 70 HU at CT, Yes = either calcification or high attenuation on nodes at CT.

Table 4

Size and Internal Characteristics of Lymph Nodes at CT for True-Positive and False-Negative Interpretations at PET/CT

Interpretation	Unidentified	Node < 5 mm		5 mm ≤ Node < 8 mm		8 mm ≤ Node < 10 mm		Node ≥ 10 mm	
		No	Yes	No	Yes	No	Yes	No	Yes
True-negative (n = 513)	267	101	26	71	27	2	13	1	5
False-negative (n = 32)	9	13	1	6	2	0	1	0	0
Total (n = 545)	275	114	27	77	29	2	14	1	5

Note.—Unidentified = no visible nodes in corresponding nodal station at CT, No = neither benign calcification nor internal diffuse high attenuation on nodes greater than 70 HU at CT, Yes = either calcification or high attenuation on nodes at CT.

CT scans are related to the presence of metastasis in normal-sized lymph nodes (17–20). On the other hand, false-positive CT findings have been related to lymph node enlargement due to benign processes.

According to meta-analyses (21–23), the sensitivity and specificity of PET for mediastinal nodal staging are in the ranges of 79%–84% and 89%–91%, respectively. The sensitivity of 79% is much higher than that of 42% in our study. However, the results of the meta-analyses stemmed from patients with mixed T (tumor) stages of lung cancer; in other words, the studies included various stages of primary tumor, whereas in our study only stage T1 lung cancer was included. Therefore, our study may have had low sensitivity because more nodes of microscopic metastasis with small size were included, which contributed to the lowering of sensitivity of integrated PET/CT. Conversely, in our study, PET/CT had a 100% specificity compared with 91% in a meta-analysis.

In one study with patients with stage I (T1 and T2N0M0) NSCLC at CT (24), the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for mediastinal nodal metastasis at FDG PET on a per-patient basis were 100%, 92%, 40%, 100%, and 93%, respectively. However, in that study, mediastinal nodes were positive only in four (5%) of 84 patients, much lower than those (16%–21%) in reports in patients with stage T1 lung cancer (3–5). Moreover, the size or visibility of true-positive mediastinal nodes at CT was not described in that study. Magnani et al (25) reported that integrated PET/CT results in improved sensitivity, specificity, and overall accuracy (78%, 95%, and 89%, respectively) in detection of malignant lymph nodes, compared with visually correlated PET and CT findings (67%, 95%, and 86%, respectively). The greater accuracy and sensitivity of integrated PET/CT has been corroborated by several studies (13,14,26,27).

This improved sensitivity of integrated PET/CT over that of CT results from the depiction of small-sized metastatic lymph nodes of less than 10 mm in short-axis diameter. The limitation of size-based nodal characterization systems at CT is well documented; up to 21% of nodes smaller than 10 mm have been reported to be malignant and up to 40% of nodes 10 mm or larger have been reported to be benign (28,29).

Despite the fact that integrated PET/CT helps improve the accuracy of mediastinal nodal staging, its resolution is still insufficient for detection of microscopic lymph node metastases (13). For example, if radionuclide uptake is not increased at PET, then integrated PET/CT cannot provide further information. In the current study, 52 (95%) of 55 pathologically malignant nodal stations were smaller than 10 mm in short-axis diameter at CT. Integrated PET/CT allowed malignancy detection only in 20 (38%) of 52 malignant nodal stations with nodes smaller than 10 mm in short-axis diameter. Thirty-two metastases to nodes smaller than 10 mm in diameter were missed in 18 patients, which lowered the sensitivity for mediastinal nodal prediction to 42%. These results suggest that integrated PET/CT does

not obviate mediastinoscopy for mediastinal nodal staging.

Interestingly enough, the positive predictive value of integrated PET/CT for the detection of mediastinal nodal metastasis in our study was 100%. Therefore, lymph nodes in stage T1 NSCLC, even though smaller than 10 mm in diameter at CT, that show positive uptake without calcification or high attenuation (>70 HU) are highly suggestive of nodal metastasis.

Because there were no false-positive interpretations, mediastinoscopy may conceivably be omitted in patients with stage T1 NSCLC who have identifiable nodes without calcification or high attenuation and increased uptake at PET/CT. However, the proportion of patients with true-positive findings for mediastinal nodal metastasis at integrated PET/CT, precluding mediastinoscopic examination, is just around 10% (in our study, 16 of 150 patients).

Increased glucose uptake by a benign node can be caused by either reactive hyperplasia or granulomatous inflammation, which may be indistinguishable from malignancy. Therefore, it is difficult to differentiate benign lymph nodes and malignant lymph nodes at CT or FDG PET alone. Shim et al (14) asserted that nodes with calcification or higher attenuations than that of the surrounding great vessels, although the nodes showed positive uptake at PET, are benign. These nodes show follicular hyperplasia in the cortex, anthracotic pigmentation, and macrophage infiltration with or without fibrotic micronodule formation in the medulla. These inflammatory changes of follicular hyperplasia and macrophage infiltration may increase glucose uptake. Therefore, nodes containing calcification or with higher attenuation than the surrounding great vessels, even with positive PET uptake, should be regarded as benign, especially in endemic areas of chronic granulomatous disease. Similarly, in the present study, 94% (46 of 49) of nodes with calcification or high attenuation and high uptake at PET proved to be benign.

Our study had limitations. First, surgeons were guided in the dissection of some specific nodal stations according to preoperative CT or integrated PET/CT findings, which may have added verification bias. Second, calcified lymph nodes and nodes with higher attenuation than the surrounding great vessels with high uptake at PET/CT may have contained focal areas of true malignancy. However, these nodes were regarded as benign during PET/CT interpretations, which presumably decreased the sensitivity of modalities in terms of depicting malignancy. We believe, however, that in endemic areas of granulomatous disease, this kind of interpretation best enhances the accuracy of lung cancer staging by reducing false-positive interpretations. Third, at our institution, PET scans were obtained 45 minutes after an intravenous injection of 370 MBq (10 mCi) of FDG. With a larger dose (555 MBq [15 mCi]) of FDG and later imaging (90 minutes after injection), a better target-to-background ratio would be obtained, thus increasing mediastinal nodal FDG uptake. However, later imaging means increased examination time and decreased patient throughput. Fourth, the interpretation of PET/CT images was performed by one radiologist and one of two nuclear medicine physicians. The same one nuclear medicine physician was not always available to take part in all PET/CT readings. This (two different nuclear medicine physicians) may have introduced a potentially confounding variable. However, both nuclear medicine

Figure 3

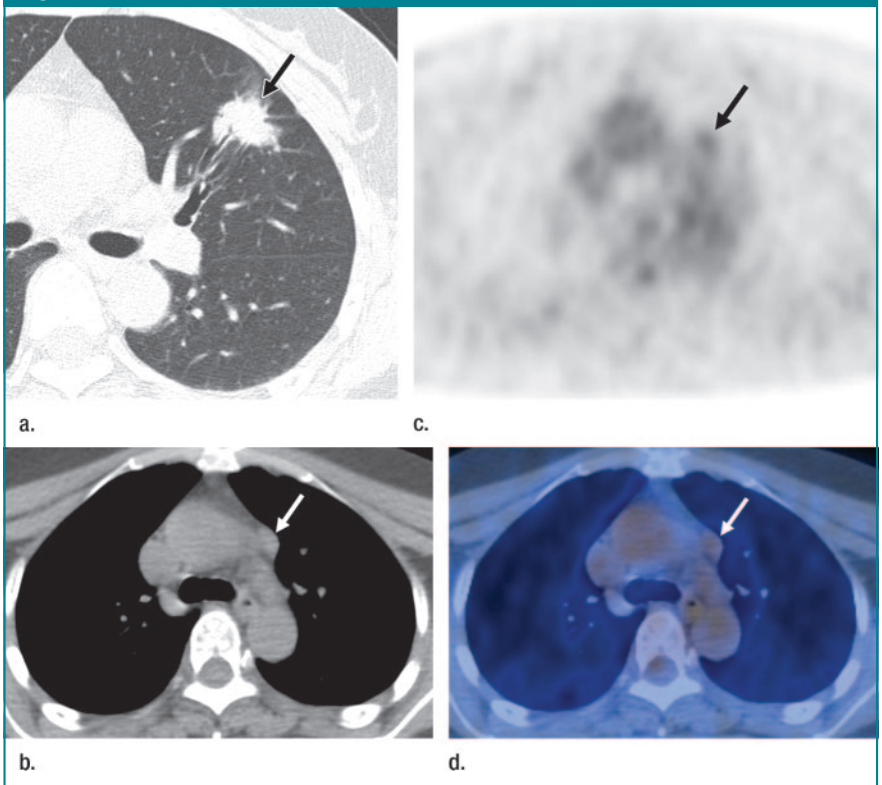

Figure 3: False-negative mediastinal lymph node metastasis at integrated PET/CT in 55-year-old woman with adenocarcinoma of the lung. **(a)** Lung window view of transverse CT scan (2.5-mm collimation, 170 mA) shows 25-mm nodule (arrow) with lobulated and spiculated margins in left upper lobe. **(b)** Mediastinal window view of transverse unenhanced CT scan (5.0-mm collimation, 80 mA) at level of azygos arch shows 8-mm (short-axis diameter) lymph node (arrow) in paraaortic area (nodal station 6). Transverse **(c)** PET and **(d)** integrated PET/CT scans at level similar to **b** demonstrate paraaortic node (arrow) showing little FDG uptake (maximum SUV = 2.0). Node was interpreted as benign and proved to be malignant at histopathologic examination of dissected nodes.

physicians had the same number of years of PET/CT interpretation experience at the same institution, and the same radiologist was always present at the time of interpretation.

In summary, in stage T1 NSCLC, mediastinal nodes in our study were positive for malignancy at histologic examination in 23% (34 of 150) of patients and 10% (55 of 568) of nodal stations. By providing morphologic and functional information, FDG PET/CT enhances the diagnostic accuracy of mediastinal nodal staging in T1 NSCLC; on a per-patient basis, it has a 100% positive predictive value and an 87% negative predictive value. However, it still has a low sensitivity (47%) for the detection of mediastinal nodal metastasis.

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