Mediastinal Nodal Staging of Nonsmall Cell Lung Cancer Using Integrated ^{18}F-FDG PET/CT in a Tuberculosis-Endemic Country

Diagnostic Efficacy in 674 Patients

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BACKGROUND. Integrated ^{18}fluorine fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has shown somewhat variable sensitivity and specificity for mediastinal nodal staging in granulomatous disease endemic areas. The purpose of the study was to prospectively evaluate the efficacy of PET/CT for mediastinal nodal staging in nonsmall cell lung cancer (NSCLC) patients in a tuberculosis-endemic country.

METHODS. Prospective assessment of the diagnostic efficacy of integrated PET/CT for detecting mediastinal nodal metastasis was performed in 674 patients (M:F ratio = 502:172; mean age, 61 years) with NSCLC. Patients underwent an integrated PET/CT examination and subsequent surgical nodal staging (by mediastinoscopy only in 121 patients and by thoracotomy in 553). Nodes showing greater ^{18}F-FDG uptake than mediastinum at PET without benign calcification or high attenuation >70 household unit (HU) at unenhanced CT were regarded as being positive for malignancy. The histologic nodal assessment results were used as reference standards.

RESULTS. Of 2477 mediastinal nodal stations evaluated in 674 patients, 275 (11%) stations in 180 (27%) patients proved to be malignant. On a per-person basis, the overall sensitivity, specificity, and accuracy of PET/CT for mediastinal nodal staging were 61% (110 of 180), 96% (473 of 494), and 86% (583 of 674), respectively. On a per-nodal station basis, they were 46% (126 of 275), 98% (2154 of 2202), and 92% (2280 of 2477).

CONCLUSIONS. Integrated PET/CT provides high specificity and reasonably high accuracy, but somewhat low sensitivity for mediastinal nodal staging of NSCLCs. The high specificity is achieved at the expense of sensitivity by interpreting calcified nodes or nodes with high attenuation at CT, even with high FDG uptake at PET, as benign in a tuberculosis-endemic region. ***Cancer*** **2007;109:1068–77.**

KEYWORDS: lung neoplasms, CT, PET, staging.

Precise mediastinal nodal staging using image modalities in nonsmall cell lung cancer (NSCLC) is mandatory for guiding subsequent staging procedures and treatment. Although computed tomography (CT) has been widely used to evaluate tumor size and adjacent structure invasion preoperatively, a number of studies have shown that CT has its shortcomings when used for lymph node staging.[1–5] Overall, CT has a sensitivity of 41% to 63%, a specificity of 43% to 57%, and an accuracy of 39% to 59% for the detection of mediastinal nodal metastasis.[2,3,5,6] These low values are probably at-

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tributable to defining node positivity using 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.[1,2,7]

^{18}Fluorine fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scans may be more sensitive than CT because alterations in tissue metabolism generally precede anatomic changes. The sensitivity of PET according to a meta-analysis of the studies published in the 1990s is 79% to 84% for the detection of mediastinal nodal metastasis in lung cancer and its specificity is 89% to 91%.[8] However, in regions of granulomatous disease ^{18}F-FDG PET may have substantially reduced accuracies mainly because PET scans show falsely increased ^{18}F-FDG uptake (high false-positive rates and thus low specificity) in inflammatory nodes, which may be observed in lymph nodes containing calcification or showing higher attenuations than those of surrounding great vessels on unenhanced CT scans.[9–12]

By providing morphologic and functional information, ^{18}F-FDG PET/CT enhances the diagnostic accuracy of mediastinal nodal staging in NSCLC. In particular, in regions endemic for granulomatous disease the CT component of integrated PET/CT (by producing attenuation values for lymph nodes on unenhanced images) is helpful for characterizing mediastinal nodes showing high ^{18}F-FDG uptake on PET images. Nodes that show high ^{18}F-FDG uptake on PET images, but with high attenuation or calcification, have been shown to be benign in >90% of cases.[11,12] According to 1 report, integrated PET/CT has a sensitivity of 80% on a nodal station basis (16 of 20 nodal stations) and a specificity of 90% (224 of 250) for mediastinal nodal staging in a tuberculosis (TB)-endemic region.[11] However, according to another report from the same institution, in which mediastinal nodal staging accuracy was evaluated in patients with T1 (tumor ≤3 cm in diameter) NSCLC, PET/CT has a lower sensitivity of 42% (23 of 55 nodal stations), but a specificity of 100% (513 of 513).[12] Therefore, it appears that integrated PET/CT has shown somewhat variable sensitivity and specificity in areas endemic for granulomatous disease. Thus, the purpose of this study was to evaluate the diagnostic efficacy of integrated PET/CT for detecting mediastinal nodal metastasis in a large number of patients with various T stages of NSCLCs in a TB-endemic area.

MATERIALS AND METHODS

Our Institutional Review Board approved the study and written informed consent was obtained from all patients for this prospective study.

Patient Population

This study was performed in a tertiary referral center of a TB-endemic country, where TB is still a serious public health problem and the incidence of active TB was as high as 73 per 100,000 population (intermediate burden country according to World Health Organization classification) in 2005.[13] A total of 756 patients referred for surgery between March 2003 and March 2006 were included and all underwent conventional lung cancer staging, based on clinical information, stand-alone chest CT (enhanced study with intravenous injection, 100 mL [Iopamidol, Iopamiron 300; Bracco, Milan, Italy]), and an integrated whole-body PET/CT study.

Forty-one patients were excluded because conventional staging studies or integrated whole-body PET/CT suggested extrathoracic metastasis; 26 were also excluded from further study because they received chemotherapy (n = 6) or chemoradiotherapy (n = 20) before surgical staging at another hospital; and an additional 15 were excluded because they had carcinoids (n = 5) or salivary gland type tumors (n = 10, mucoepidermoid carcinoma in 6 and adenoid cystic carcinoma in 4). Thus, 674 patients (502 men and 172 women, age range, 30–90 years; mean, 61 years) were included and all underwent surgical staging. The mean interval between the initial histologic diagnosis of NSCLC and integrated PET/CT was 2 days (range, 0–5 days; median, 3 days), whereas that between integrated PET/CT and surgical staging was 13 days (range, 1–42 days; median, 7 days). Nodal stages were classified according to the American Joint Committee on Cancer staging systems.[14] Histopathologic results served as the reference standards. Of these 674 patients, 218 (32%) had a past medical history of pulmonary tuberculosis as determined by clinical or imaging studies.

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 ensuring a normal blood glucose level (≤150 mg/dL) in peripheral blood,[15] patients received an intravenous injection of 370 MBq of ^{18}F-FDG and then rested for approximately 45 minutes before undergoing imaging. Image acquisition was performed using an integrated PET/CT device (Discovery LS, GE Healthcare, Milwaukee, WI) consisting of an Advance NXi PET scanner and an 8-slice Light Speed Plus CT scanner. The axes of both systems were mechanically aligned so that shifting the examination table by 68 cm moved the patient from the CT gantry into the PET gantry.

CT was performed from the head to the pelvic floor using a standardized protocol involving 140 kV, 80 mAs, 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 axial 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 and allow image fusion, and CT transmission maps were generated. PET-image datasets were reconstructed iteratively using the ordered subsets expectation maximization algorithm and by applying the segmented measured attenuation correction (2 iterations, 28 subsets) to CT data. Coregistered images were displayed using eNTEGRA software (GE Medical Systems), which enabled image fusion and analysis.

Prospective Integrated PET/CT Image Analysis

One chest radiologist and 1 nuclear medicine physician, both unaware of clinical, stand-alone CT and pathologic results, together prospectively evaluated integrated PET/CT datasets. Decisions were reached by consensus. Nodal stations were evaluated by allocating them to 9 groups as described by the lymph node map definition for lung cancer staging proposed by Mountain and Dresler[16]: station 1, highest mediastinal (1R: right, 1L: left); station 2, upper paratracheal (2R: right, 2L: left); station 3, prevascular and retrotracheal; station 4, lower paratracheal (4R: right, 4L: left); station 5, subaortic (aortopulmonary window); station 6, paraaortic (ascending aorta or phrenic); station 7, subcarinal; station 8, paraesophageal; and station 9, pulmonary ligament (9R: right, 9L: left). Mediastinal nodes with an increased glucose uptake and a distinct margin were considered positive for malignancy. Nodes were regarded to have an increased glucose uptake when they demonstrated ^{18}F-FDG uptake at a level greater that that of the surrounding mediastinal tissue.[11,12] Mediastinal nodes were divided into 4 categories according to the integrated PET/CT results, namely, 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 regarded as present when nodular, laminated, or diffuse and when the attenuation was ≥200 household unit (HU). A highly attenuating node was defined as one that appeared to have a higher attenuation than mediastinal vascular structures with an attenuation of ≥70 HU using an region of interest (ROI)-based measurement. Even if glucose uptake was high (higher than the background activity), calcified lymph nodes or lymph nodes with a higher attenuation than surrounding great vessels on the CT images of integrated PET/CT were regarded as benign.[11,12]

Surgical and Histopathologic Analysis

Surgical staging included mediastinoscopy (n = 121), mediastinoscopy plus thoracotomy (n = 309), and thoracotomy alone (n = 244). Patients (n = 121) who underwent mediastinoscopy only were classified into a mediastinoscopy-only group. Those (n = 553), who underwent thoracotomy with or without mediastinoscopy were classified into a thoracotomy group. Surgical staging was performed by 1 of 4 experienced thoracic surgeons (all had more than 10 years of experience). In 121 patients only mediastinoscopic nodal staging results were available because curative resection was deferred due to the presence of positive nodes indicating neoadjuvant concurrent chemoradiation therapy (n = 108) or because patients denied surgery (n = 13) in spite of negative nodes on mediastinoscopic evaluation. Tumor resection and extensive mediastinal lymph node dissection with thoracotomy were performed on 553 patients. Thoracotomy was performed after considering the results of preoperative imaging examinations, ie, stand-alone CT and integrated PET/CT.

During mediastinoscopy, the 2R, 4R, 2L, 4L, and 7 ATS lymph node map areas were routinely sampled and during thoracotomy, according to our routine surgical protocol, surgeons dissected all visible and palpable lymph nodes accessible in the mediastinum irrespective of size. Specifically, all encountered lymph nodes were removed from 10R, 9, 8, 7, 4R, 3, and 2R the ATS lymph node map areas for tumors of the right lung and from areas 10L, 9, 8, 7, 6, 5, and 4L for the left lung. When necessary, especially when an imaging study suggested possible nodal metastasis in other nodal stations other than those included in routine lymph node dissection, group 1 (highest mediastinal) or 2L (when tumors were located in the left lung) nodes were also evaluated during mediastinoscopy or thoracotomy.

In the 553 patients of surgical tumor resection group, 389 patients in whom the primary tumor was limited to a lobe underwent lobectomy. Seventy-two patients underwent bilobectomy, 14 sleeve lobectomy, and 78 pneumonectomy because the primary tumor was straddling the fissure or there were associated hilar lymph nodes with extracapsular invasion.

Surgeons coded dissected lymph nodes using a numbering system based on the lymph node map definition for lung cancer staging proposed by Mountain and Dresler.[16] Subsequently, a pathologist evaluated nodes numbered in surgical fields and recorded the presence or absence of tumor in these nodes. The pathologist also described tumors (ie, histopathologic class, size, surrounding organ involvement, necrosis, and distance from resection margin) if thoracotomy was performed. Specimens were stained with hematoxylin/eosin and examined by light microscopy.

A pathologic stage was recorded for each patient and a total of 2477 nodal stations were dissected in the 674 patients.

Retrospective PET/CT Evaluation

This study was performed to retrospectively assess the relation between ^{18}F-FDG uptake values within identified mediastinal nodes and their sizes or morphologic features (benign calcification and diffuse high attenuation within nodes) of the nodes. Two chest radiologists, also unaware of stand-alone CT and pathologic results, and who did not take part in the initial PET/CT interpretation, evaluated the CT and PET components of integrated PET/CT after the surgical staging had been completed. Decisions on findings were reached by consensus. On CT component images they recorded the short-axis diameters of detected lymph nodes in the mediastinum. Nodal stations were evaluated by allocating them to 9 groups using the lymph node map definition for lung cancer staging as was used previously to interpret integrated PET/CT images. The following information was also recorded for all detected nodes: the presence of a benign calcification (nodular, laminated, or diffuse) or diffuse high attenuation (>70 HU) within nodes. On PET component images the 2 radiologists measured the maximum standard uptake values (SUVs) of all nodal stations if these nodal stations had identifiable ^{18}F-FDG uptake.

Statistical Analysis

Sensitivities, specificities, and accuracies for the detection of malignant mediastinal lymph nodes were assessed overall and according to tumor T stages on a per-patient basis and on a per-nodal station (9 stations) basis. Detection rates of nodal metastasis by integrated PET/CT were compared according to the various T stages using the Fisher exact test.

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 nodes with a calcification or high attenuation at CT and high uptake at PET, we evaluated how well benign nodes with these characteristics at integrated PET/CT were classified as benign.

For nodal stations that harbored metastasis pathologically, but had low ^{18}F-FDG uptake values, we measured and recorded maximum SUV values at PET and their short-axis diameter at CT when such nodal stations were identifiable at PET/CT. The presence of any correlation between the size and the maximum SUV of these nodes was tested using Pearson correlation coefficiency analysis.

RESULTS

Lung Cancer Histology

Histologic analysis demonstrated adenocarcinoma in 333 patients, squamous cell carcinoma in 271, large cell neuroendocrine carcinoma in 29, bronchioloalveolar carcinoma in 14, adenosquamous cell carcinoma in 7, unspecified nonsmall-cell carcinoma in 5, and sarcomatoid carcinoma in 15 (pleomorphic carcinoma in 14 and spindle cell carcinoma in 1). One hundred sixty-nine patients had T1 cancer, 417 T2, 43 T3, and 45 T4.

Nodes: ^{18}F-FDG Uptake

A total of 2477 nodal stations were sampled (mean number of nodal stations sampled per patient, 3.7). These were 18 highest mediastinal (nodal station 1), 287 upper paratracheal (2), 902 lower paratracheal (4), 64 prevascular and retrotracheal (3), 197 subaortic (aortopulmonary, 5), 51 paraaortic (6), 620 subcarinal (7), 42 paraesophageal (8), and 296 pulmonary ligament nodes (9) by pathologic examination. Of these, 275 nodal groups (11%) proved to be positive for malignancy in 180 (27%) of 674 patients. The positives were 2 highest mediastinal, 32 upper paratracheal, 5 prevascular and retrotracheal, 112 lower paratracheal, 23 subaortic, 5 paraaortic, 87 subcarinal, 1 paraesophageal, and 8 pulmonary ligament nodes (Table 1).

Statistical Parameters

In terms of depicting malignant nodes, on a per-patient basis the overall sensitivity, specificity, accuracy, and positive and negative predictive values of integrated PET/CT were 61% (110 of 180 patients with positive nodes) (Fig. 1), 96% (473 of 494 with negative nodes) (Fig. 2), 86% (583 of 674), 84% (110 of 131), and 87% (473 of 543), respectively. Corresponding values in various T stages are summarized

TABLE 1
PET/CT Classification of Lymph Node Groups Shown to be Histologically Positive by Biopsy or Resection

	Nodal stations									
	1	2	3	4	5	6	7	8	9	Total
False-negative at PET/CT	2	22	3	62	10	4	40	1	5	149
True-positive at PET/CT	0	10	2	50	13	1	47	0	3	126
Number of truly positive nodal groups/number of nodal groups evaluated	2/18	32/287	5/64	112/902	23/197	5/51	87/620	1/42	8/296	275/2477

PET indicates positron emission tomography; CT, computed tomography.
Group 1, highest mediastinal; group 2, upper paratracheal; group 3, prevascular and retrotracheal; group 4, lower paratracheal; group 5, subaortic (aorto-pulmonary window); group 6, para-aortic (ascending aorta or phrenic); group 7, subcarinal; group 8, paraesophageal; group 9, pulmonary ligament.

in Table 2. Sensitivities were not different among the various T stages ($P = .294$), but the specificities ($P = .002$) and accuracies ($P = .006$) were significantly different and better in lower T stages.

On a per-nodal station basis the sensitivity, specificity, accuracy, and positive and negative predictive values of integrated PET/CT were 46% (126 of 275 nodal stations), 98% (2154 of 2,202), 92% (2280 of 2477), 72% (126 of 174), and 98% (2154 of 2303), respectively. One hundred forty-nine false-negative interpretations (in 70 patients) were rendered by PET/CT for 84 paratracheal (nodal stations 2 and 4), 40 subcarinal, 10 subaortic, 5 pulmonary ligament, 4 paraaortic, 3 prevascular, 1 paraesophageal, and 2 highest mediastinal nodal stations. Forty-eight false-positive interpretations (in 21 patients) were rendered at PET/CT for 27 paratracheal (nodal stations 2 and 4), 14 subcarinal, 5 subaortic, 1 paraaortic, and 1 paraesophageal nodal stations (Table 1).

Nodes: High Attenuation or Calcification at CT

One hundred seven (83%) of 129 nodes with either calcification (n = 99, 95 nodular and 4 laminated) or high attenuation >70 HU (n = 30) and high uptake on PET (up to maximum SUV, 11.7) were true negatives by pathologic examination (Fig. 3), whereas the remaining 22 (17%) turned out to be false-negatives. On a per-person basis, 60 (77%) of 78 patients having nodes with either a calcification (n = 59, 56 nodular and 3 laminated) or high attenuation >70 HU (n = 19) and high uptake by PET (up to maximum SUV, 11.7) were true-negative nodes by pathologic examination, whereas the remaining 18 (23%) turned out to be false-negatives.

When we regarded nodes with either a calcification or high attenuation >70 HU (n = 129) and high uptake at PET as metastasis-positive, sensitivity on a per-person basis went up to 71% (128 of 180 patients) but specificity and accuracy fell to 84% (413 of 494) and 80% (541 of 674), respectively.

Maximum SUVs and Their Sizes for Nodes Showing False-Negative Values at PET/CT

Of the 149 false-negative nodes, 22 (15%) had a calcification or higher attenuation >70 HU at CT and high ^{18}F-FDG uptake at PET (mean maximum SUV = 5.0; range, 3.5–7.5). Their mean size was 9 mm (range, 5–13 mm) in short-axis diameter at CT. Of these 149 nodes 127 (85%) had no identifiable ^{18}F-FDG uptake (n = 87, 58%) or uptake less than the mediastinum (n = 40 [27%], mean maximum SUV values, 2.2; range, 1.3–3.2). The mean size of these 40 nodes with ^{18}F-FDG uptake less than the mediastinum was 7 mm (range, 4–14 mm) in short-axis diameter at CT. There was no correlation between the size and maximum SUV of these 40 false-negative nodes ($r = 0.110$, $P = 0.499$; Pearson correlation coefficiency analysis).

DISCUSSION

In the present study sensitivity (61% on a per-person basis) was somewhat lower than reported previously.[8,17–19] Several explanations may be proposed. First, we included a large number of patients with a surgically resectable NSCLC in whom mediastinal nodal evaluations were performed surgically. Thus, many more patients with early-stage NSCLC (patients with T1 and T2 diseases accounted for 87% [586 of 674 patients] of all patients) were included. Thus, patients with high T stage of disease and overt mediastinal nodal metastasis by imaging studies, including integrated PET/CT, may have been excluded, and therefore patients with microscopic nodal metastasis were more selectively included. Second, to enhance specificity in a granulomatous disease endemic region, we regarded nodes with high

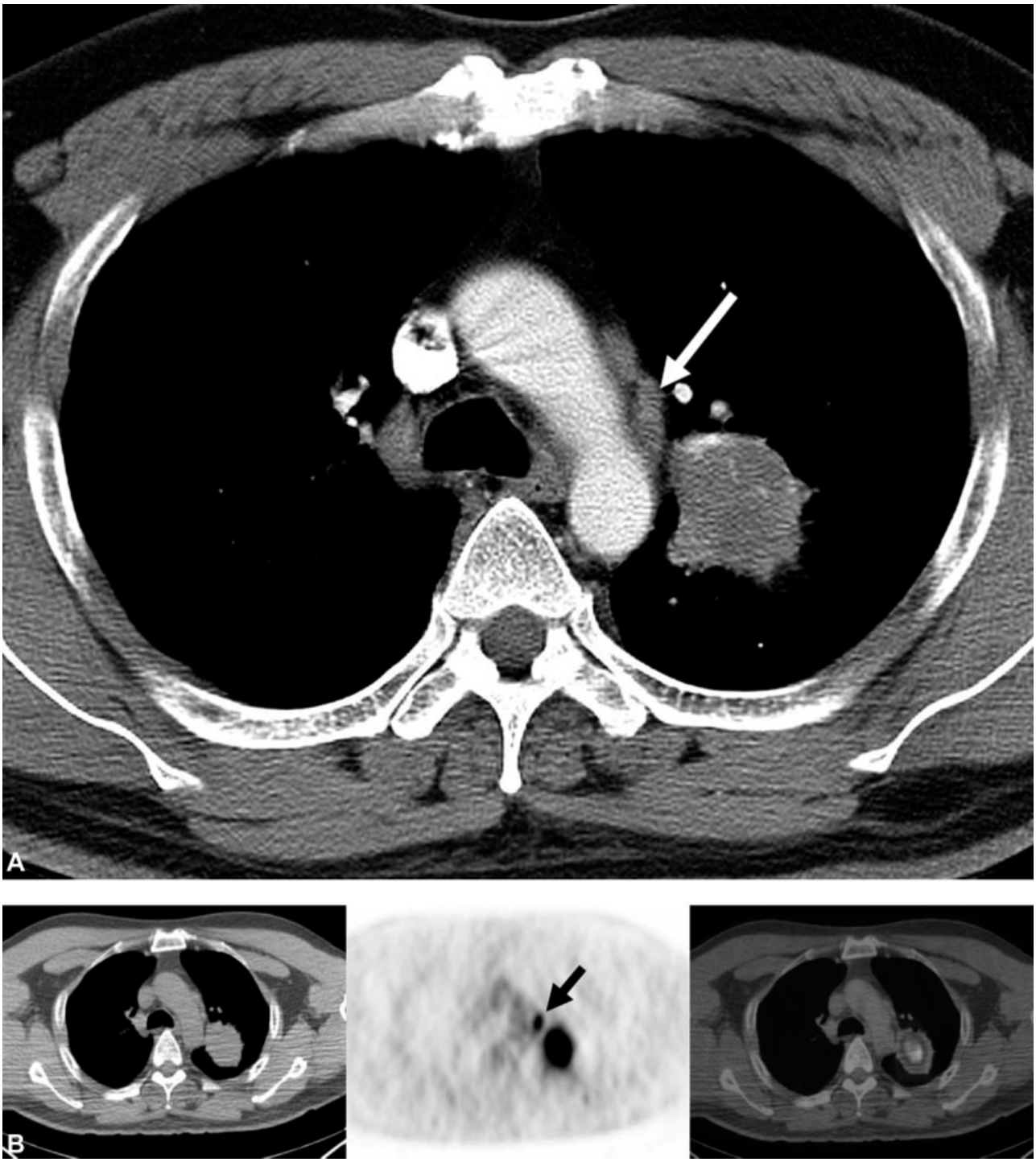

FIGURE 1. True-positive mediastinal lymph node metastasis at integrated PET/CT in a 53-year-old man with lung adenocarcinoma. (A) Mediastinal-window transverse enhanced CT scan (5.0-mm collimation, 170 mA) obtained at level of azygos arch shows 3.6-cm-sized mass in left upper lobe and 6.0-mm-sized lymph node (arrow) in short-axis diameter in aortopulmonary window area (nodal station, 5). (B) Integrated PET/CT scans obtained at a similar level to a demonstrate node showing strongly increased FDG uptake (maximum SUV = 7.4) (arrow) suggesting malignant node, which proved to contain metastatic adenocarcinoma cells.

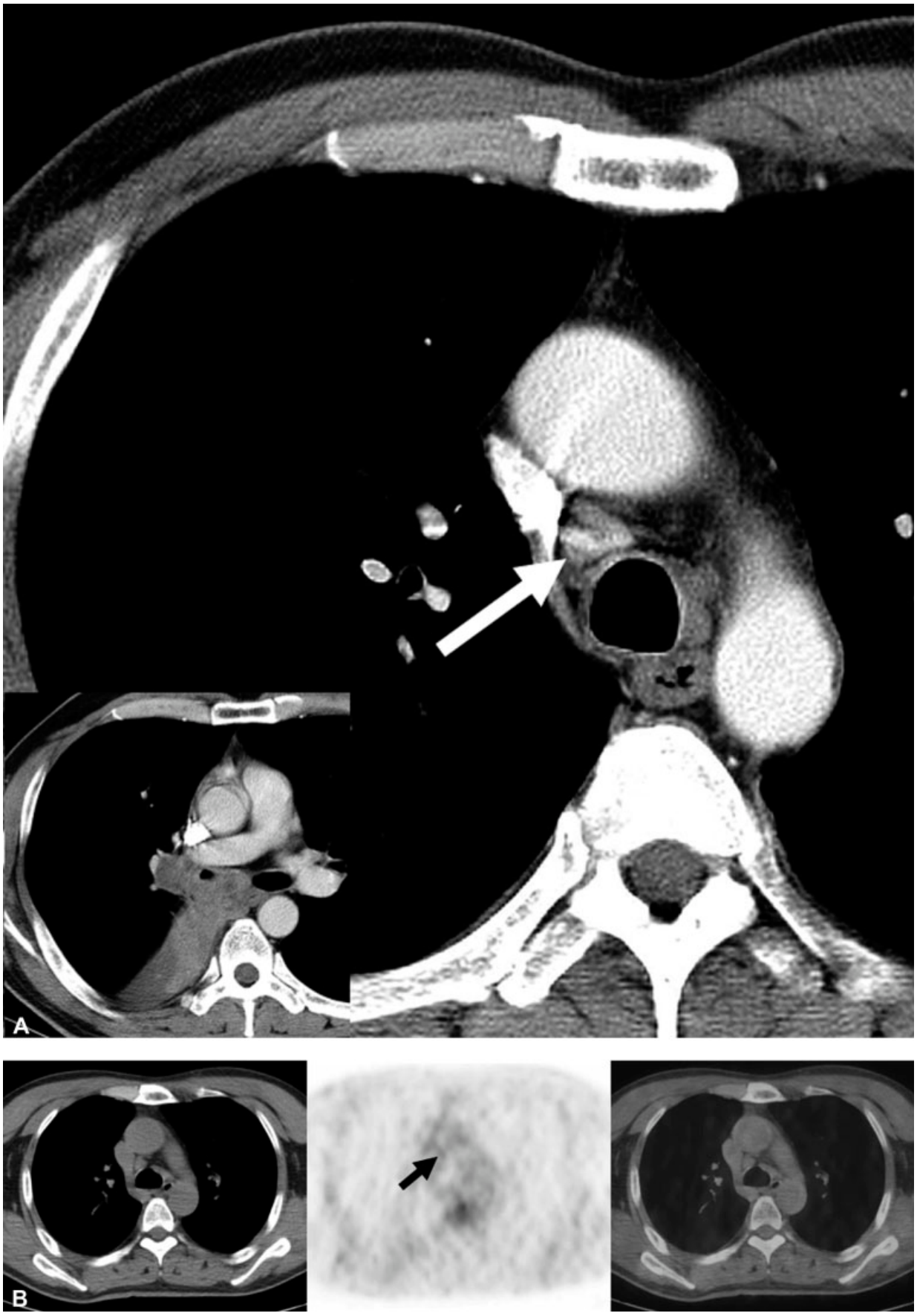

FIGURE 2. True-negative mediastinal lymph node metastasis at integrated PET/CT in a 55-year-old man with lung squamous cell carcinoma. (A) Mediastinal-window transverse enhanced CT scan (5.0-mm collimation, 170 mA) obtained at the level of the azygos arch shows 10-mm-sized lymph node (arrow) in short-axis diameter in right lower paratracheal area (nodal station, 4R). Inset: T2 squamous cell carcinoma with ipsilateral hilar nodal metastasis. (B) Integrated PET/CT scans obtained at similar level to a demonstrate right lower paratracheal node showing mild FDG uptake (maximum SUV = 1.6) (arrow). This node was interpreted as benign and proved to be benign on histopathologic examination.

TABLE 2
Diagnostic Efficacy of Integrated PET/CT According to on a Per-Patient Basis and on a Per-Nodal Station Basis

	Per-patient basis, %				Per-nodal station basis, %		
T stages	Sensitivity	Specificity	Accuracy	T stages	Sensitivity	Specificity	Accuracy
T1 (n = 169)	59 (19/32)	100 (137/137)	92 (156/169)	T1 (n = 587)	41 (20/49)	99 (533/538)	94 (553/587)
T2 (n = 417)	66 (76/116)	94 (283/301)	86 (359/417)	T2 (n = 1584)	50 (89/179)	98 (1370/1405)	92 (1459/1584)
T3 (n = 43)	47 (7/15)	100 (28/28)	81 (35/43)	T3 (n = 156)	50 (9/18)	99 (137/138)	94 (146/156)
T4 (n = 45)	47 (8/17)	89 (25/28)	73 (33/45)	T4 (n = 150)	28 (8/29)	94 (114/121)	81 (122/150)
Overall (n = 674)	61 (110/180)	96 (473/494)	86 (583/674)	Overall (n = 2477)	46 (126/275)	98 (2154/2202)	92 (2280/2477)

PET indicates positron emission tomography; CT, computed tomography.

FDG uptake but with calcification or high attenuation on CT images as benign. In fact, of these 129 nodal stations only 83% (107 nodal stations) proved to be benign. Twenty-two nodes contained an area of focal metastasis. On a per-person basis, 60 (77%) of 78 patients with such nodes appeared to have true-negative nodes, whereas the remaining 18 (23%) turned out to be false-negatives and these false-negatives reduced the sensitivity.

As a trade-off, our study shows a high specificity (96% on a per-person basis). In previous studies, specificities of PET in distinguishing malignant nodes were in the ranges of 89% to 91%. As mentioned above, our regarding nodes with high FDG uptake but with calcification or high attenuation on CT images as benign may have increased specificity.

When we compared the diagnostic efficacies of integrated PET/CT for mediastinal nodal metastasis detection among the various T stages no significant differences in sensitivity were found. Intuitively, we expected that sensitivity would rise for cases with higher T-stage disease, because in these cases rates of mediastinal nodal metastasis are higher than in cases with lower T-stage diseases. However, similar sensitivities were obtained for various T stages, which suggest that ^{18}F-FDG PET is inherently limited in terms of the detection of microscopic mediastinal nodal metastasis. This is probably due to the low intrinsic resolution (currently an in-plane resolution of 5 mm) of ^{18}F-FDG PET for the detection of microscopically metastatic mediastinal nodes.[20]

Because of the limited sensitivity of PET/CT for the detection of small-sized nodal metastases, one might suggest lowering ^{18}F-FDG uptake cutoff values to detect small metastatic mediastinal nodes. However, in the present study, of 149 nodal stations false-negative for malignancy, discrete ^{18}F-FDG uptake was identifiable only in 42% (62 of 149) of such stations. Moreover, these identifiable nodes demonstrated variable sizes (mean, 7 mm; range, 4–14 mm) in their short-axis diameters and there was no significant correlation between the size and maximum SUV in these identifiable nodes. Thus, applying different cutoff values for ^{18}F-FDG uptake (node-size-dependent maximum SUV cutoff criteria) for small-sized nodes does not seem advisable.

Nodes with a calcification or with high attenuation (>70 HU), despite positive uptake, have a much higher probability of being benign rather than metastatic. In previous studies most nodes showed follicular hyperplasia in the cortex and anthracotic change and macrophage infiltration with or without fibrotic micronodular changes by pathologic examinations. However, some nodes (about 5% to 6% of nodal stations; 1 of 20 nodal stations in 1 study and 3 of 49 nodal stations in other study) contained metastatic foci.[11,12] In the current study somewhat higher percentages of such nodes (17% on a per nodal station basis and up to 23% on a per person basis) had concurrent microscopic metastasis, thus lowered sensitivity for detecting malignant nodes. However, if we count these positive uptake nodes with a calcification or with high attenuation as malignant nodes a marked lowering of specificity and thus of accuracy (in our study 84% [413 of 494] and 80% [541 of 674], respectively) would be expected.

In the current study 27% (180 of 674) of patients with NSCLC and 11% (275 of 2477) of nodal stations had mediastinal nodal metastasis. Integrated PET/CT showed high negative predictive values; on a per-person basis, 87% (473 of 543 patients), and on a per-nodal station basis, 98% (2154 of 2303 nodal stations). These high negative predictive values suggest some important diagnostic and therapeutic implications. Namely, patients with negative mediastinal nodes at integrated PET/CT may undergo a curative surgical treatment with omission of mediastinoscopy.

Our study has several limitations. First, it suffers from selection bias, because we included patients that received only surgical mediastinal nodal dissec-

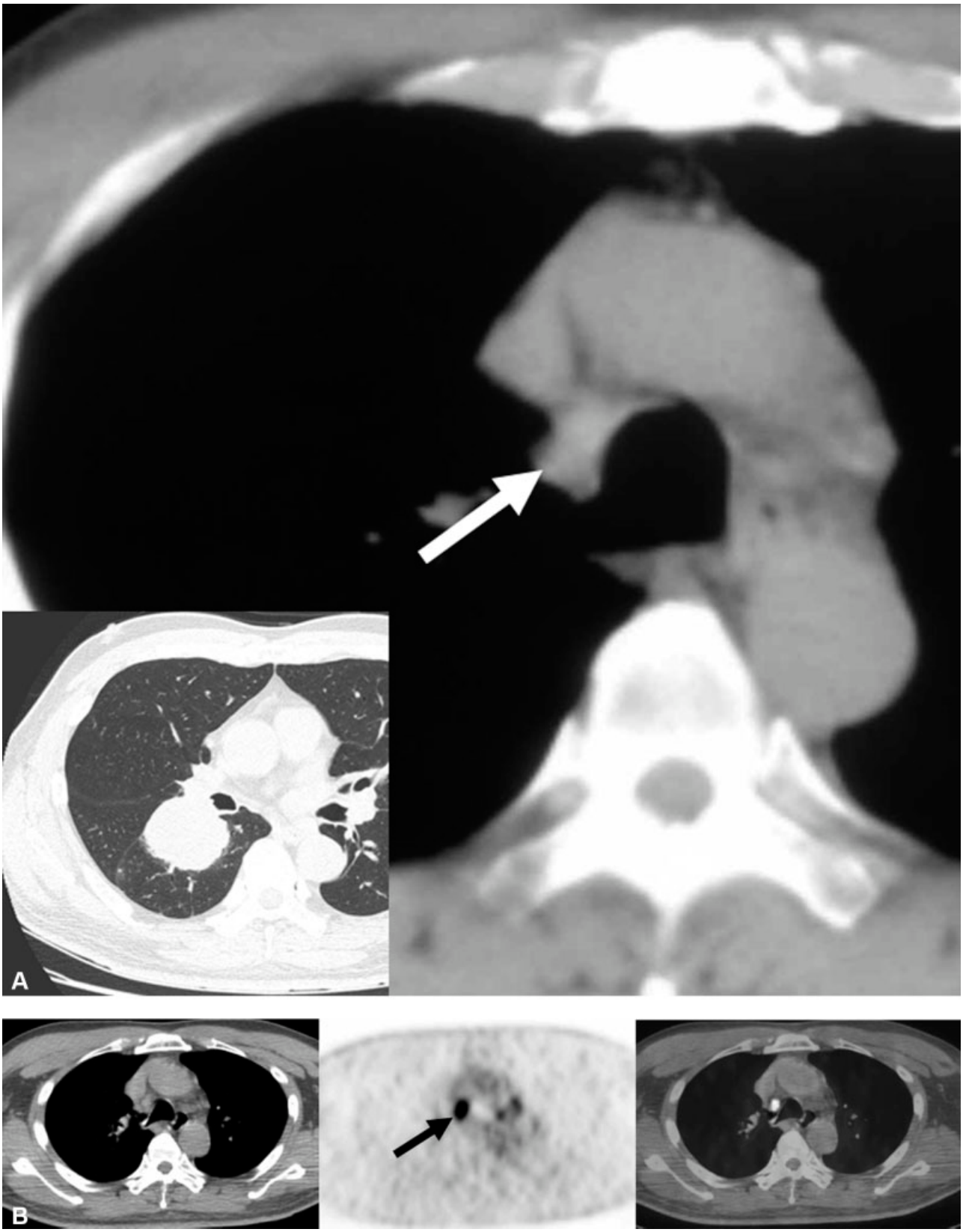

FIGURE 3. True-negative mediastinal lymph node metastasis at integrated PET/CT in a 65-year-old man with lung large cell neuroendocrine carcinoma. (Top) Mediastinal window transverse unenhanced CT (5.0-mm collimation, 80 mA) scan obtained at level of right upper lobar bronchus shows 12-mm-sized lymph node in short-axis diameter (arrow) in right lower paratracheal area. Node demonstrates higher attenuation than mediastinal vascular structures. Inset: 5.3-cm-sized T2 lung cancer in right lower lobe. (B) Integrated PET/CT scans obtained at similar level to (A) demonstrate markedly increased FDG uptake (maximum SUV = 9.4) (arrow). This node was interpreted as benign and proved to be benign on histopathologic examination.

tion or mediastinoscopic nodal biopsy. Therefore, as mentioned above, many more cases of early stage of NSCLCs were included, which may have contributed to observed sensitivity reduction. Second, the dissections of some specific nodal stations were guided by preoperative CT or integrated PET/CT findings, which might have induced a verification bias.

We concluded that integrated PET/CT provides high specificity and reasonably high accuracy, but relatively low sensitivity for the mediastinal nodal staging of NSCLCs, the high specificity being achieved at the expense of sensitivity by interpreting calcified nodes or nodes with high attenuation at CT, even with high FDG uptake at PET, as benign in a tuberculosis endemic region.

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