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ORIGINAL ARTICLE

^{18}F-FDG PET/CT in mediastinal lymph node staging of non-small-cell lung cancer in a tuberculosis-endemic country: consideration of lymph node calcification and distribution pattern to improve specificity

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Abstract
Purpose The aim of the study was to assess the accuracy of ^{18}F-fluorodeoxyglucose (FDG) PET/CT in mediastinal lymph node staging of patients with non-small-cell lung cancer (NSCLC) in a region with a high prevalence of granulomatous disease.
Methods Between March 2004 and February 2006, all patients with NSCLC underwent FDG PET/CT and contrast-enhanced thoracic CT, and subsequent surgical resection. PET/CT and contrast-enhanced CT images of 182 patients (126 men and 56 women; mean age 60.7 years) with NSCLC were acquired. Mediastinal node staging was determined using the American Joint Committee on Cancer (AJCC) staging system. Surgical and histological findings served as the reference standard.
Results A total of 182 patients with 778 mediastinal node stations were evaluated. Sensitivity and specificity of contrast-enhanced CT were 36% and 80% on a per-patient basis and 23% and 92% on a per-node station basis. Sensitivity and specificity of PET/CT were 81% and 73% on a per-patient basis and 75% and 85% on a per-node station basis. After lymph nodes with calcification and bilateral hilar distribution were considered benign, sensitivity and specificity of PET/CT were 75% and 89% on a per-patient basis and 66% and 96% on a per-node station basis.
Conclusion This prospective study suggests that FDG PET/CT can more accurately stage mediastinal lymph nodes than CT. Considering lymph node calcification and distribution pattern could improve specificity at the cost of a decrease in sensitivity.

Keywords Lung cancer · Positron emission tomography (PET) · ^{18}F-Fluorodeoxyglucose (FDG) · Staging

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Introduction

The stage of non-small-cell lung cancer (NSCLC) is based on the TNM classification defined by the American Joint Committee on Cancer (AJCC), and an obvious relationship between tumor stage and survival rate of patients has been shown in several studies [1–3]. In particular, metastasis to N2 lymph nodes is considered to be crucial for operability because patients without lymph node metastases or only intrapulmonary or hilar lymph node metastases can receive surgery. For patients with positive N2 lymph nodes, neoadjuvant chemotherapy with surgery or concurrent or sequential chemoradiotherapy are legitimate choices [4, 5]. Even though contrast-enhanced CT has been the most

common imaging modality for TNM staging, it has limitations in evaluating lymph node status because prediction of positive lymph nodes on CT is based on size criteria alone. Contrast-enhanced CT shows low to moderate sensitivity and specificity for assessment of mediastinal lymph node metastases [6–8].

^{18}F-Fluorodeoxyglucose (FDG) PET is a functional imaging modality that is based on the increased glucose metabolism of malignant cells [9, 10]. In several previous studies, FDG PET has been shown to be effective in detecting mediastinal lymph node metastases in patients with lung cancer and more sensitive and specific than CT [1, 2, 11–14]. However, anatomic information concerning tumor cells is limited on FDG PET images and the resolution is insufficient to detect small lymph node metastases. Further, false-positive findings from inflammatory or granulomatous lesions are still problematic on FDG PET images in regions with a high prevalence of granulomatous disease.

Since the introduction of PET/CT, functional information and morphological information can be combined on lymph node staging with ease. It has been reported that the high specificity is achieved at the expense of sensitivity by interpreting calcified nodes seen on CT as benign [15, 16]. The purpose of this study was to assess the diagnostic accuracy of integrated FDG PET/CT in mediastinal lymph node staging of NSCLC compared to contrast-enhanced thoracic CT, and to evaluate the characteristics of false-positive lymph nodes on FDG PET/CT to improve specificity.

Materials and methods

Patient selection

Between March 2004 and February 2006, 182 patients who underwent preoperative FDG PET/CT and subsequent surgical resection of NSCLC were enrolled prospectively. The study group comprised 126 men and 56 women with a mean age of 60.7±10.8 years. All patients underwent a contrast-enhanced CT scan of the thorax and FDG PET/CT scan as part of staging work-up. Patients with metastatic lesions on preoperative PET/CT images were excluded from this study. Furthermore, patients who had had neoadjuvant chemotherapy or radiotherapy for contralateral or bulky mediastinal node metastases before thoracotomy or mediastinoscopy were also excluded.

Contrast-enhanced thoracic CT

Contrast-enhanced CT scans were performed using a Somatom Plus 4 (Siemens Medical Solutions) and a HighSpeed Advantage scanner (GE Healthcare). After noncontrast CT had been performed, each patient received 120 ml of nonionic contrast material (Ultravist 370; Schering) through an 18-gauge catheter inserted into a forearm vein. Contrast material was injected at 3 ml/s using an automatic power injector (CT 9000 ADV digital injection system; Liebel-Flarsheim). After injection of contrast material, the contrast-enhanced CT scan was done. CT images were routinely obtained with the patient in the supine position during full inspiration. CT was performed using a single-detector scanner and the following parameters: 5-mm collimation, 5-mm reconstruction interval, and 1:1 table pitch. Transverse images were reconstructed with a soft-tissue algorithm. X-ray tube voltage was 120–140 kV and the current varied between 240 and 260 mA.

Integrated PET/CT

PET/CT was performed using a Gemini PET/CT system (Philips, Milpitas). All patients fasted for at least 6 h before the PET/CT scan and only glucose-free water was allowed. An intravenous injection of 5.18 MBq of FDG/kg of body weight was administered and patients rested for 60 min before imaging. PET/CT data were obtained with patients in the supine position. Emission images were acquired after CT scanning, and an emission scan was performed in nine bed positions with 2.5 min per step. Attenuation correction was done based on CT data, and the data were resized from a 512×512 matrix to a 128×128 matrix to match the PET emission data for image fusion. PET data were reconstructed using the 3-D row action maximum likelihood iterative reconstruction algorithm (RAMLA).

Image evaluation

All CT images were evaluated by an experienced radiologist and all PET/CT images were evaluated by two experienced nuclear medicine physicians. Mediastinal node stations were evaluated in nine groups according to the lymph node stations for lung cancer staging introduced by Mountain and Dresler and adopted by the AJCC [17, 18]: station 1, highest mediastinal; station 2, upper paratracheal; station 3, prevascular and retrotracheal; station 4, lower paratracheal; station 5, subaortic or aorticopulmonary; station 6, paraaortic (ascending aortic or phrenic); station 7, subcarinal; station 8, paraesophageal; and station 9, pulmonary ligament. Nodes on the boundary between node stations were assigned to a more cephalic location. During evaluation of CT images, the short axis of mediastinal lymph nodes was measured and positive nodes were defined as those with a short-axis diameter greater than 1 cm.

In addition to size, the presence of calcification was considered on noncontrast CT images. Integrated PET/CT images were evaluated visually. The maximum standardized uptake values (maxSUVs) were measured in all lymph nodes with increased FDG uptake. The location and maxSUV of primary tumors were also recorded.

First, mediastinal lymph nodes with focally increased FDG uptake higher than mediastinal blood pool uptake were judged as positive, taking the SUVs of the lymph nodes into consideration. On a second interpretation of PET/CT images, calcified high-attenuation lymph nodes (defined as nodes with higher attenuation than that of the mediastinal vascular structures and more than 70 HU on noncontrast CT images) were interpreted as benign, irrespective of FDG uptake [16, 19]. Furthermore, bilateral symmetric paratracheal nodes on FDG PET images with a hilar or interlobar nodal distribution with similar FDG uptake or mediastinal nodes with a symmetric hilar or interlobar nodal distribution with similar FDG uptake were also judged as benign. Even though the attenuation of some lymph nodes with a typical distribution pattern was lower than 70 HU, all the lymph nodes in the patients with this pattern were interpreted as benign.

Surgical procedures and surgical/pathological stage

Thoracotomy was performed in 169 of 182 patients (93%). Mediastinoscopic biopsy without thoracotomy was performed in the remaining 13 patients (7%) because of a pathological high N stage found on mediastinoscopic biopsy. An additional mediastinoscopic biopsy was performed in 31 of the 169 patients in whom thoracotomy was performed, and the remaining 138 patients had thoracotomy only. All the mediastinal nodes which were positive on FDG PET/CT images or on contrast-enhanced CT images were sampled or dissected at thoracotomy and/or mediastinoscopic biopsy. All the specimens were examined by an experienced pathologist, and surgical/pathological staging was assigned according to the criteria of the International System for Staging Lung Cancer [20].

Data analysis

The results of contrast-enhanced CT and FDG PET/CT were compared with the histopathological findings. Subsequently, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were determined. Additionally, a receiver operating characteristic (ROC) curve was generated by SPSS software (SPSS, Chicago, IL) to determine the maxSUV for detecting mediastinal lymph node metastases.

Results

Histopathological analysis

The characteristics of the enrolled patients are shown in Table 1. Mediastinal lymph node metastases were documented in 36 of the 182 patients (20%). Of these 36 patients, 18 (50%) had adenocarcinoma, 15 (41%) had squamous cell carcinoma, 1 (3%) had large-cell carcinoma, 1 (3%) had adenosquamous carcinoma, and 1 (3%) had pleomorphic carcinoma. Positive nodes were found in 19% (18/93) of those with adenocarcinoma and in 23% (15/66) of those with squamous cell carcinoma.

A total of 778 mediastinal lymph node stations were dissected. There were 4 highest mediastinal (station 1), 112 upper paratracheal (station 2), 22 prevascular and retrotracheal (station 3), 209 lower paratracheal (station 4), 58 subaortic (station 5), 58 paraaortic (station 6), 170 subcarinal (station 7), 13 paraesophageal (station 8), and 132 pulmonary ligament (station 9) lymph nodes. Of the 778 mediastinal node stations, 53 (7%) showed positive nodes.

Evaluation of mediastinal node status by CT and PET/CT

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FDG PET/CT in detecting mediastinal lymph node metastases were 81% (29/36), 73% (106/146), 42% (29/69), 94% (106/113), and 74% (135/182) on a per-patient basis, and 75% (40/53), 85% (616/725), 27% (40/149), 98% (616/629), and 84% (656/778), on a per-node station basis, respectively. After considering lymph node calcification and distribution

Table 1 Characteristics of the 182 patients

Characteristic	Value
Age (years)	60.7±10.8
Pathology, *n* (%)	
Adenocarcinoma	93 (51)
Squamous cell carcinoma	66 (36)
Large-cell carcinoma	7 (4)
Bronchoalveolar carcinoma	5 (3)
Nonspecified cancer	11 (6)
T-stage, *n* (%)	
T1	72 (40)
T2	102 (56)
T3	8 (4)
Size of mediastinal lymph nodes (cm)	0.7±0.3
N-stage, *n* (%)	
N0 or N1	146 (80)
N2	36 (20)

pattern, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of FDG PET/CT in detecting mediastinal lymph node metastases were 75% (27/36), 89% (130/146), 63% (27/43), 94% (130/139), and 86% (157/182) on a per-patient basis, and 66% (35/53), 96% (695/725), 54% (35/65), 98% (695/713), and 94% (730/778) on a per-node station basis, respectively (Tables 2 and 3).

The ROC curve based on the maxSUV of lymph nodes is shown in Fig. 1. The maxSUV of nodes had an area under the ROC curve (AUC) of 0.751 (95% CI 0.693–0.803) before consideration of calcification and distribution pattern with a cut-off maxSUV of 2.1, and had an AUC of 0.873 (95% CI 0.825–0.911) after consideration of calcification and distribution pattern with a cut-off maxSUV of 2.2. The AUC of the ROC curve after consideration of calcification and distribution pattern was significantly higher than that before correction ($p<0.05$).

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of contrast CT were 36% (13/36), 80% (116/146), 30% (13/43), 84% (116/139), and 71% (129/182) on a per-patient basis, and 23% (12/53), 92% (670/725), 18% (12/67), 94% (670/711), and 88% (682/778) on a per-node station basis, respectively (Tables 4 and 5). Of 36 patients with histopathologically positive nodes, 12 were true-positive on both contrast-enhanced CT and PET/CT, 15 were true-positive on PET/CT but false-negative on CT (Fig. 2), 1 was true-positive on CT but false-negative on PET/CT (Fig. 3), and 8 were false-negative on both CT and PET/CT. In addition, of 16 patients with false-positive PET/CT findings, 4 showed granulomatous changes in the mediastinal lymph nodes on histopathology (Fig. 4).

Analysis of maxSUV and size in lymph nodes

Of 53 metastatic node stations, 35 were true-positive on FDG PET/CT. The mean maxSUV of the 35 true-positive node stations was 5.0±3.4 (range 2.2–17.4) and the mean value of all other node stations in which FDG uptake was seen was 3.1±1.1 (range 1.2–7.4). The mean maxSUV of true-positive node stations was significantly higher than the mean of the others ($p<0.01$). Additionally, the mean maxSUV (11.0±8.8) of primary tumors with positive nodes was significantly higher than the mean value (8.1±6.2) of those with negative nodes ($p<0.05$).

Among the 35 mediastinal lymph nodes that were positive on FDG PET/CT, 24 (69%) were less than 8 mm, 5 (14%) were between 8 and 12 mm, and 6 (17%) were greater than 12 mm in diameter. The size of true-positive lymph nodes on FDG PET/CT was between 5 and 16 mm. The mean maxSUV of true-positive lymph nodes on PET/CT with a diameter less than 8 mm was 3.6±1.1, of those with a diameter between 8 and 12 mm was 5.9±2.7, and of those with a diameter greater than 12 mm was 9.9±5.6. The mean maxSUV of lymph nodes significantly increased as size increased ($p<0.05$).

Table 2 FDG PET/CT findings in the 182 patients on a per-patient basis

PET/CT		Histopathology	
		Positive	Negative
Before correction[a]	Positive	29	40
	Negative	7	106
After correction[a]	Positive	27	16
	Negative	9	130

[a] Correction means consideration of lymph node calcification and distribution pattern.

Table 3 FDG PET/CT findings in 778 node stations on a per-node station basis

PET/CT		Histopathology	
		Positive	Negative
Before correction[a]	Positive	40	109
	Negative	13	616
After correction[a]	Positive	35	30
	Negative	18	695

[a] Correction means consideration of lymph node calcification and distribution pattern.

Discussion

In this prospective study, we demonstrated that FDG PET/CT had better diagnostic accuracy in staging NSCLC than contrast-enhanced thoracic CT in regions with a high prevalence of granulomatous disease. The latest nationwide tuberculosis survey in Korea, which was done in 1995, showed that the prevalence of active pulmonary tuberculosis was still as high as 1.0%, and smear- and/or culture-positive cases were 219 per 100,000 of the population [21]. Because chronic inflammatory disease such as tuberculosis can lead to false-positive findings of mediastinal nodal metastases, recent studies have assessed diagnostic performance of FDG PET in a tuberculosis-endemic country [16, 22]. In this study, we used specific FDG PET/CT criteria considering nodal calcification and distribution pattern to improve the positive predictive value in patients in a tuberculosis-endemic country.

Contrast-enhanced CT is commonly used for staging NSCLC but it has many limitations. According to a meta-analysis of 20 studies with 3,438 patients, sensitivity,

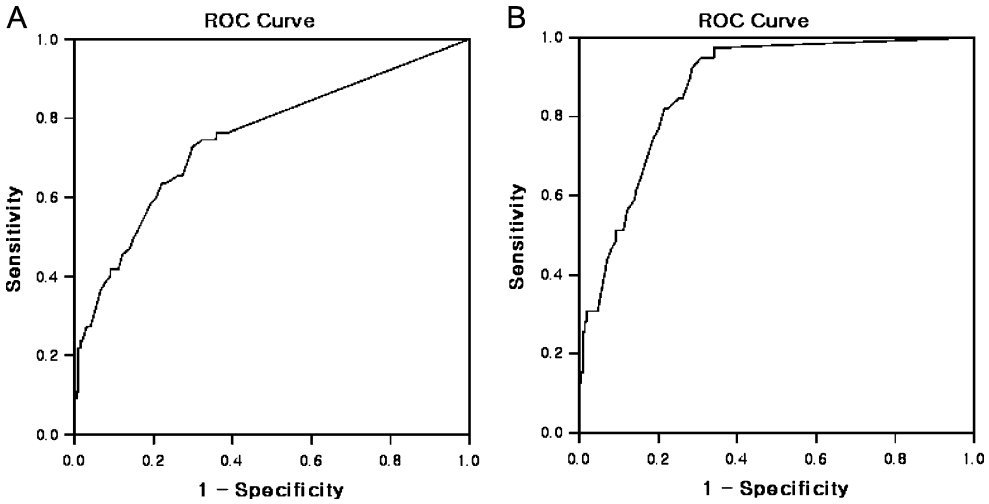

Fig. 1 ROC curves based on maxSUV of mediastinal lymph nodes. **a** Before correction for distribution pattern, the AUC was 0.751 (95% CI 0.693–0.803). **b** After correction for distribution pattern, the AUC was 0.873 (95% CI 0.825–0.911)

specificity, positive predictive value, and negative predictive value were 57%, 82%, 56%, and 83%, respectively [23]. In addition, there was marked heterogeneity in sensitivity and specificity between studies. Compared to these results, the sensitivity (36%) and positive predictive value (30%) in our study were much lower than in previous studies. The low sensitivity of CT in this study may have been associated with study group selection. Patients who underwent neoadjuvant chemotherapy were excluded, patients with true-positive nodes and with large lymph nodes were not included in the study group. However, our results revealed the limitations of contrast-enhanced CT in detecting mediastinal node metastases in the selected patient group.

According to previous studies [1, 2, 11–16], the sensitivity of FDG PET for staging mediastinal lymph node metastases ranges from 61% to 89% and the specificity ranges from 83% to 96%. In nearly all previous studies, FDG PET has proved to be more accurate than CT and very high negative predictive values have been reported. Integrated PET/CT has proven to be more effective than PET. Cerfolio et al. [24] found that integrated PET/CT is a better overall predictor of lymph node status than PET alone (78% versus 56%). Lardinois et al. [25] showed that N stage classification of patients using PET/CT (88%) is significantly more likely to be correct than when using PET alone (40%) and when using visual correlation of PET and CT (65%). Our study showed good performance of PET/CT compared to contrast-enhanced thoracic CT and showed high specificity and negative predictive value, similar to previous studies; however, sensitivity and positive predictive value were moderate and somewhat lower, and the sensitivity and positive predictive value on a per-node station basis were even lower. Hence, FDG PET cannot totally replace the need for mediastinoscopy for confirmation of mediastinal nodes. However, the low sensitivity and positive predictive value might have resulted from the prevalence of metastatic mediastinal nodes in our study (20% on a per-patient basis and 7% on a per-node station basis), which was slightly lower than that in previous studies (23–31% on a per-patient basis and 10–11% on a per-node station basis) [13, 16, 19].

In several reviews, the false-negative rate of PET in detecting mediastinal node metastasis ranges from 5% to 7% [2, 26, 27]. One reason for these false-negative findings is the insufficient resolution of PET for detecting microscopic lymph node metastases. This can happen when the lymph node burden of disease is minimal, and some refer to this as minimal N2 disease because it has a reasonable prognosis [12]. Another cause of false-negative findings is the fact that FDG uptake in metastatic lymph nodes cannot be distinguished from uptake in the primary tumor or adjacent positive nodes, mainly due to the limited spatial resolution of FDG PET. These factors may explain the low sensitivity of PET on a per-node station basis in our study. In addition, the probability of false-negative findings is much higher in

Table 4 Contrast-enhanced thoracic CT findings in the 182 patients on a per-patient basis

CT	Histopathology	
	Positive	Negative
Positive	13	30
Negative	23	116

Table 5 Contrast-enhanced thoracic CT findings in 778 node stations on a per-node station basis

CT	Histopathology	
	Positive	Negative
Positive	12	55
Negative	41	670

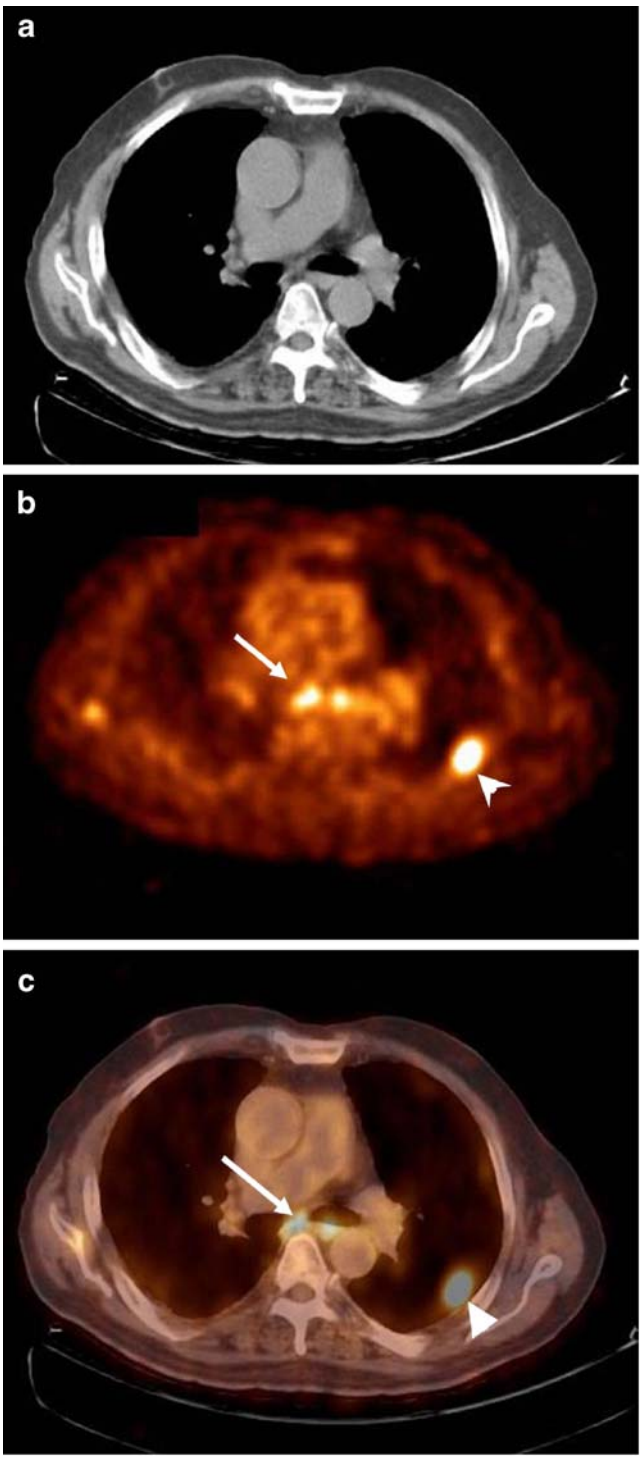

Fig. 2 Images obtained in a 69-year-old man diagnosed with large-cell carcinoma in the left upper lobe. **a** CT image shows a small lymph node in the subcarinal area but because of its small size, metastasis was excluded. **b** PET image shows increased glucose metabolism in the mediastinum (*arrow*) and left upper lobe (*arrowhead*). **c** Fused PET/CT image shows increased glucose metabolism in the subcarinal lymph nodes (*arrow*) and left upper lobe (*arrowhead*). After mediastinoscopic biopsy, lymph node metastases were found in the subcarinal lymph nodes

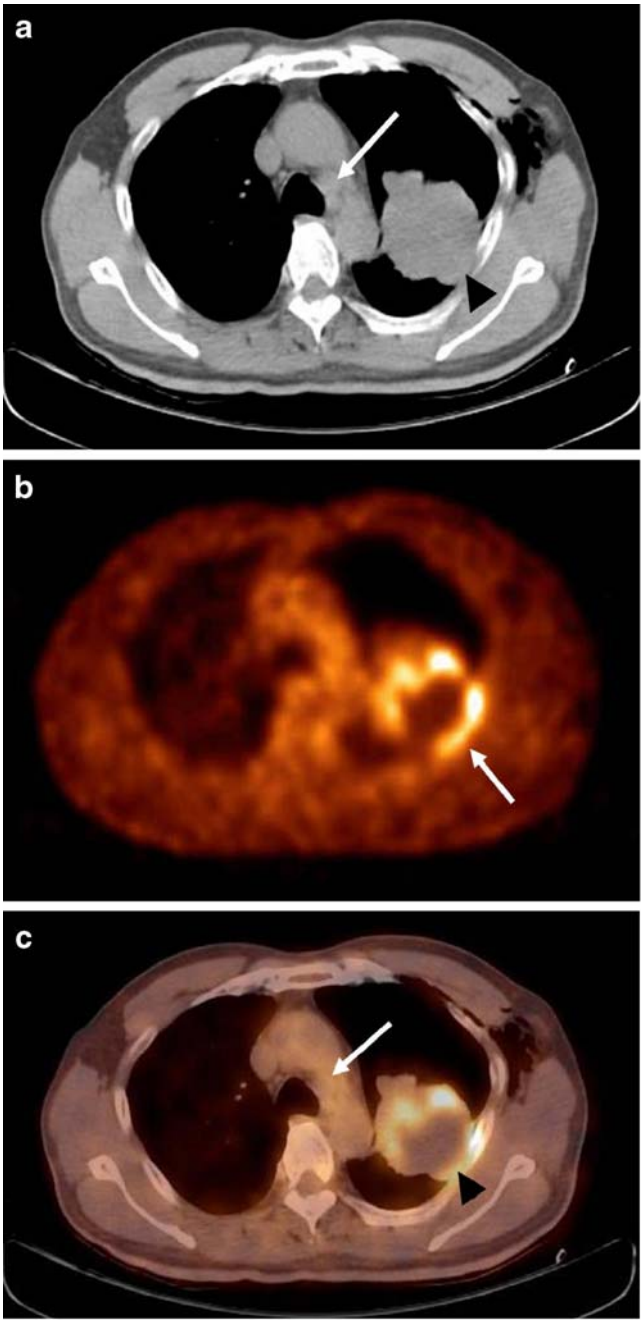

Fig. 3 Images obtained in a 54-year-old man with squamous cell carcinoma in the left upper lobe. **a** CT image shows a huge mass in the left upper lobe (*arrowhead*) with an enlarged lymph node in the left lower paratracheal area (*arrow*). **b**, **c** PET image (**b**) and fused PET/CT image (**c**) do not depict focally increased glucose metabolism in the left lower paratracheal area (**c** *arrow*). However, increased glucose metabolism with a central metabolic defect is seen in the mass lesion in the left upper lobe (**b** *arrow*, **c** *arrowhead*). After lobectomy, lymph node metastases were found in the left lower paratracheal lymph nodes

the presence of positive N1 nodes, a centrally located primary tumor, or adenocarcinoma [28, 29].

Pooling the results from previous studies, the false-positive rate of PET in detecting N2 nodes ranges from 16

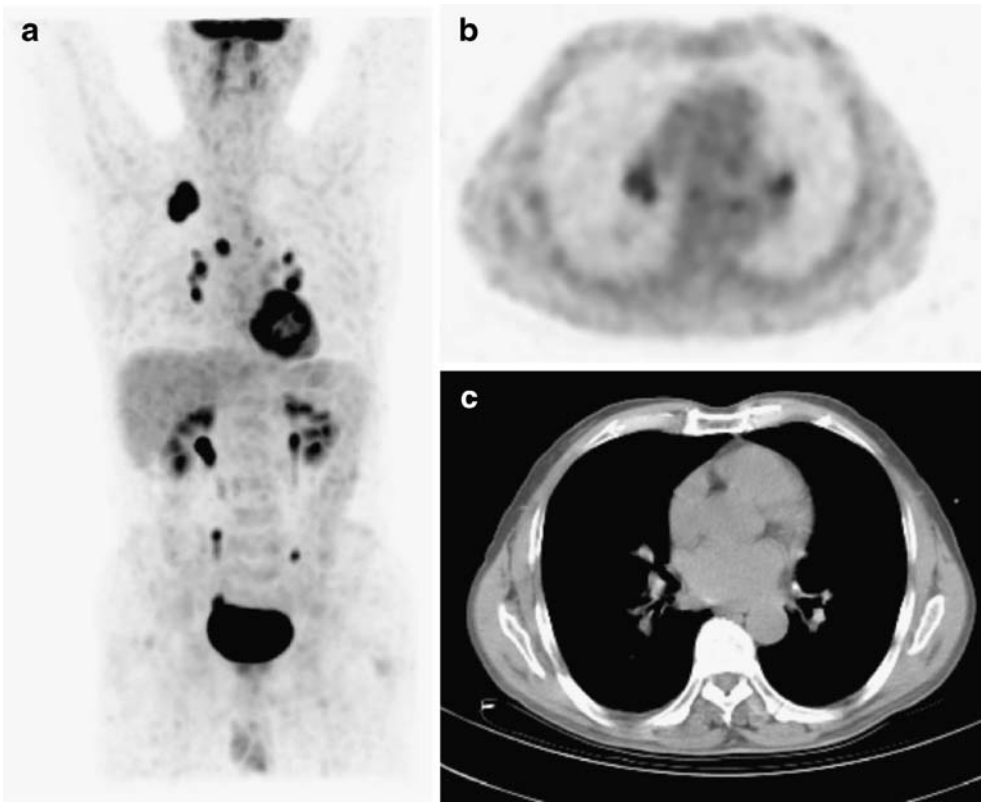

Fig. 4 Typical benign lymph node distribution pattern in a 65-year-old man with right upper lobe squamous cell cancer. **a** Projection image shows multiple bilateral hilar and interlobar lymph nodes with increased FDG uptake. Pathology showed reactive hyperplasia in every lymph node selected. **b** Axial PET image shows bilateral hilar hypermetabolism. **c** Noncontrast CT image shows calcification of bilateral lymph nodes

to 22% [21, 24]. Hence, a positive mediastinal PET result should be confirmed by mediastinoscopy or lymph node sampling. One of the main reasons for false-positive findings is benign lymph nodes containing inflammatory or granulomatous tissue with high metabolic activity. It has been reported that lung empyema, tuberculosis, sarcoidosis, talc granulomata, eosinophilic lung disease, histoplasmosis, aspergillosis, and other infections, show significant uptake of FDG [30]. In our study, four patients with false-positive nodes showed granulomatous changes in mediastinal nodes by histopathology. Considering that East Asia still has a high rate of chronic granulomatous disease including tuberculosis, especially among the elderly, false-positive findings may be a result of increased FDG accumulation in granulomatous tissue. Another cause of false-positive findings may be sampling error during surgery or mediastinoscopy. This can result in understaging, as many lymph nodes that harbor metastatic deposits appear normal during surgery [31].

We classified lymph nodes with calcification or bilateral distribution as benign. It is considered that lymph nodes with calcification should be classified as benign, irrespective of FDG uptake [15, 16, 19]. In addition, a high prevalence of hilar lymph node FDG uptake has been reported in regions with a high prevalence of granulomatous disease [32]. Our results support the view that lymph nodes with high FDG uptake and calcification could be interpreted as benign, especially when distributed bilaterally. By using the specific criteria of benign lymph nodes in our study (the calcification and distribution pattern of nodes), the positive predictive value increased by about 20% on a per-patient basis (from 42% to 63%) and by about 25% on a per-node station basis (from 27% to 54%) without losing the negative predictive value. Considering the high false-positive rate among patients in a tuberculosis-endemic country, the increase in the positive predictive value could be important clinically. However, a further prospective study with our specific criteria of benign nodes may be needed.

Of true-positive lymph nodes on FDG PET/CT, 69% were less than 8 mm, indicating that metastasis of the lymph nodes cannot be evaluated by means of size criteria. Because of these normal-sized true-positive nodes, the sensitivity of integrated PET/CT was higher than that of contrast-enhanced CT alone. It may be assumed that as the resolution of PET improves, sensitivity may increase. In our study, the mean maxSUV increased as the size of the lymph nodes increased. This was mainly due to the partial volume effect and from this fact, we should consider that metastasis in small lymph nodes would show mildly increased FDG uptake.

Our study had some limitations. First, patients who received neoadjuvant therapy before thoracotomy or mediastinoscopy were excluded from this study because the state of metastatic lymph nodes cannot be evaluated after chemotherapy. Many metastatic enlarged lymph nodes with high FDG uptake were excluded and, therefore, overall

sensitivity of PET and CT might have been higher than shown in this study. Second, not all mediastinal nodes were resected, and surgeons dissected specific node stations mainly guided by preoperative imaging studies such as contrast-enhanced CT and PET/CT. This may have been a bias of our study.

In summary, our data suggest that FDG PET/CT can more accurately stage mediastinal lymph nodes than contrast-enhanced thoracic CT by providing high specificity and negative predictive value. Taking lymph node calcification and distribution pattern into consideration was helpful in decreasing false-positive PET findings and increasing specificity.

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