Usefulness of PET with ^{11}C-Methionine for the Detection of Hilar and Mediastinal Lymph Node Metastasis in Lung Cancer

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We retrospectively evaluated the usefulness of PET with ^{11}C-methionine (methionine PET) for the diagnosis of lymph node metastases in patients with lung cancer. **Methods:** Methionine PET and CT were performed before surgical intervention in 41 patients with primary lung cancer. We evaluated individual lymph nodes by methionine PET along with corresponding CT images. The ^{11}C-methionine accumulation of lymph nodes was assessed semiquantitatively by analysis of the tumor-to-muscle ratio (TMR) and was compared with CT and histological diagnoses. **Results:** A total of 126 lymph nodes, 36 of which were histologically diagnosed as metastatic, were assessed by CT and methionine PET. The TMR in metastatic lymph nodes (n = 36) was 5.15 ± 1.69, whereas that of nonmetastatic lymph nodes (n = 90) was 2.91 ± 0.76; this difference was significant ($P < 0.0001$). The most adequate TMR cutoff value for diagnosis of metastasis based on the results of receiver operating characteristic curve analysis was 4.1. The positive and negative predictive values, sensitivity, specificity, and accuracy of methionine PET were 79.5%, 94.3%, 86.1%, 91.1%, and 89.7%, respectively, and were superior to those of CT (57.6%, $P = 0.04$; 81.7%, $P = 0.008$; 52.8%, $P = 0.002$; 84.4%, NS; and 75.4%, $P = 0.002$, respectively). All positive nodes that were shown to be true-positive by CT, and 12 of 17 false-negatives on CT were correctly diagnosed by PET. Ten of 14 lymph nodes that were false-positive on CT were also correctly diagnosed by PET. **Conclusion:** Methionine PET appears to be superior to CT for the diagnosis of lymph node metastasis in lung cancer patients. The high negative predictive value of methionine PET suggests that cases in which lymph nodes are enlarged on CT with negative PET analysis may be diagnosed as negative for metastasis.

Key Words: PET; ^{11}C-methionine; lung cancer; lymph node metastasis

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In patients with lung cancer, surgical treatment is preferable for those without lymph node metastasis or with only hilar lymph node metastasis. At present, however, there is no consensus regarding the optimal treatment regimen for lung cancer patients with mediastinal lymph node metastasis. Thus, preoperative assessment of mediastinal and hilar lymph node metastases is an important problem. CT is most commonly used for preoperative assessment of lymph node metastases, although its sensitivity and specificity are low (*1–3*). Recently, PET using FDG has been demonstrated to be useful for detecting lymph node metastases in lung cancer patients (*4–10*). The sensitivity and specificity of FDG PET were shown to be higher than those of CT. ^{11}C-methionine is another tracer for PET that can be used to assess metabolic demand for amino acids in cancer cells. ^{11}C-methionine PET (methionine PET) has been reported to be useful in differential diagnosis of benign and malignant lung tumors (*11*). In this study, we retrospectively investigated the usefulness of methionine PET for detecting mediastinal and hilar lymph node metastases in patients with primary lung cancer.

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MATERIALS AND METHODS

PET studies were performed before surgical treatment in 41 patients with primary lung cancer from October 1993 through February 1996. All patients underwent surgical treatment with resection or sampling of hilar and/or mediastinal lymph nodes. We retrospectively compared the results of methionine PET studies with those of CT and histological diagnoses of lymph nodes.

PET

Two Hitachi PCT3600W PET scanners (Hitachi Medico, Chiba, Japan) with 108-mm axial fields of view were used for all patients. Written informed consent was obtained from all patients before the PET studies. The PCT 3600W had 4 or 8 detector rings with 352 bismuth germanate crystals per ring and used direct and cross-plane coincidence detection to generate 7 slices, 15.4-mm thick, or 15 slices, 7.7-mm thick. Full width at half maximum (FWHM) was 8 mm in this study. The acquisition protocol was as follows. Patients fasted for at least 6 h before PET studies. Transmission scan was acquired for 1300 s using a rotating ^{68}Ge-plate source in all patients before emission scanning, and the total counts per slice were ≥7 × 10^6. Emission scans were obtained over a 15-min scanning period, 22 min after intravenous injection of 370 MBq ^{11}C-methionine. The total counts per slice were ≥3 × 10^6. Image reconstruction in a 128 × 128 matrix using measured attenuation correction was performed using a Shepp and Logan filter. No scatter correction was applied in this study. Patients were positioned on a bed with the upper part of the sternum adjusted to the upper border of the scanning field. Upper mediastinal, subcarinal, and hilar lymph nodes were examined in this study.

^{11}C-methionine is usually accumulated not only in the lymph nodes (both metastatic and nonmetastatic) but also in the bone marrow of the ribs, sternum, and vertebrae, and in the esophagus. However, this amino acid is not highly accumulated in the mediastinum or the chest wall. Significant accumulation of radioactivity in the mediastinal and hilar regions was considered to indicate uptake by lymph nodes. However, it is difficult to determine the location of lymph nodes by emission scanning only. We used transmission scanning images to visualize the outline of the mediastinum. We were able to visualize the location of lymph nodes on fusion images of emission and transmission scans. Reference to corresponding CT images was made to confirm precisely the location of the lymph nodes. No automated linking program for PET and CT was available in this study. This interpretation of PET and CT images was performed by an experienced radiologist. We evaluated the lymph nodes semiquantitatively on the basis of the tumor-to-muscle ratio (TMR) obtained as follows. The regions of interest (ROIs) were placed in the lymph nodes, including the highest uptake area (square ROI, 4 × 4 mm or 8 × 8 mm) and paravertebral muscle areas (square ROI, 12 × 12 mm). TMR was calculated by dividing the mean radioactivity of the tumor ROI by that of the muscle ROI. No recovery coefficient correction was applied. We constructed receiver operating characteristic (ROC) curves according to the TMR and pathological diagnosis and determined the cutoff value for diagnosis of lymph node metastasis. Predictive values, sensitivity, specificity, and accuracy of PET were calculated from this cutoff value.

CT

CT was performed before the PET study in all patients on either a Hilite Advantage (General Electric, Brookfield, WI) or a CT Vertex 3000 (Yokogawa Medical System, Tokyo, Japan). Serial sections 10 mm thick were obtained from the lung apices through the posterior costophrenic angle, using 2-s scans at 120 kV, 120 mA after intravenous injection of 100 mL nonionic contrast medium at 2 mL/s with a power injector. The short-axis diameters of lymph nodes were measured, and those >10 mm were considered positive for metastasis.

RESULTS

Patient Population

Of the 41 patients (14 women, 27 men; average age, 61.1 y; range, 42–79 y), 27 had adenocarcinomas, 10 had squamous cell carcinomas, and 4 had small cell carcinomas. Thirty-nine patients underwent lobectomy with lymph node resection, and 2 patients underwent partial resection of the primary tumor with sampling of lymph nodes (Table 1).

TABLE 1
Patient Characteristics

No. of patients	41
Sex (M/F)	27/14
Mean age (range)	61.1 y (42–79 y)
Histological type	
Adenocarcinoma	27
Squamous cell carcinoma	10
Small cell carcinoma	4
Surgical staging	
R2 lymph node resection	39
Lymph node sampling	2

Lymph Node Metastases

A total of 126 lymph nodes, of which 49 were hilar and 77 were mediastinal, were assessed by methionine PET and CT. Fourteen hilar (28.6%) and 22 mediastinal nodal stations (28.6%) were positive for metastases. There were no metastatic lymph nodes in the region in which uptake of ^{11}C-methionine was not seen.

CT Evaluation

The lymph nodes were classified into 3 groups according to their short-axis diameter: large-sized nodes were defined as those with a short axis >10 mm, regarded as positive for metastasis; medium size was defined as 6–10 mm; and small size was defined as <6 mm. Of the 126 surgically resected lymph nodes, 33 were large and 93 were of medium or small size. The positive and negative predictive values of CT were 57.6% (19/33) and 81.7% (76/93), respectively. The sensitivity, specificity, and accuracy of CT were 52.8% (19/36), 84.4% (76/90), and 75.4% (95/126), respectively (Table 2).

PET

All metastatic lymph nodes could be identified by PET analysis (Figs. 1 and 2). The TMR for histologically positive lymph nodes was 5.15 ± 1.69 (mean ± SD), whereas that for negative lymph nodes was 2.91 ± 0.76 ($P < 0.0001$, unpaired t test) (Fig. 3). ROC curve analysis for 126 lymph nodes from the hilar and mediastinal regions showed the optimal TMR cutoff point between positive and negative for metastasis to be 4.1 (Fig. 4). The positive and negative predictive values of methionine PET based on this criterion

TABLE 2
Lymph Node Status by CT

	CT*	
Histology	Positive	Negative
Positive, 36	19	17
Negative, 90	14	76

*Positive predictive value, 57.6%; negative predictive value, 81.7%; sensitivity, 52.8%; specificity, 84.4%; accuracy, 75.4%.

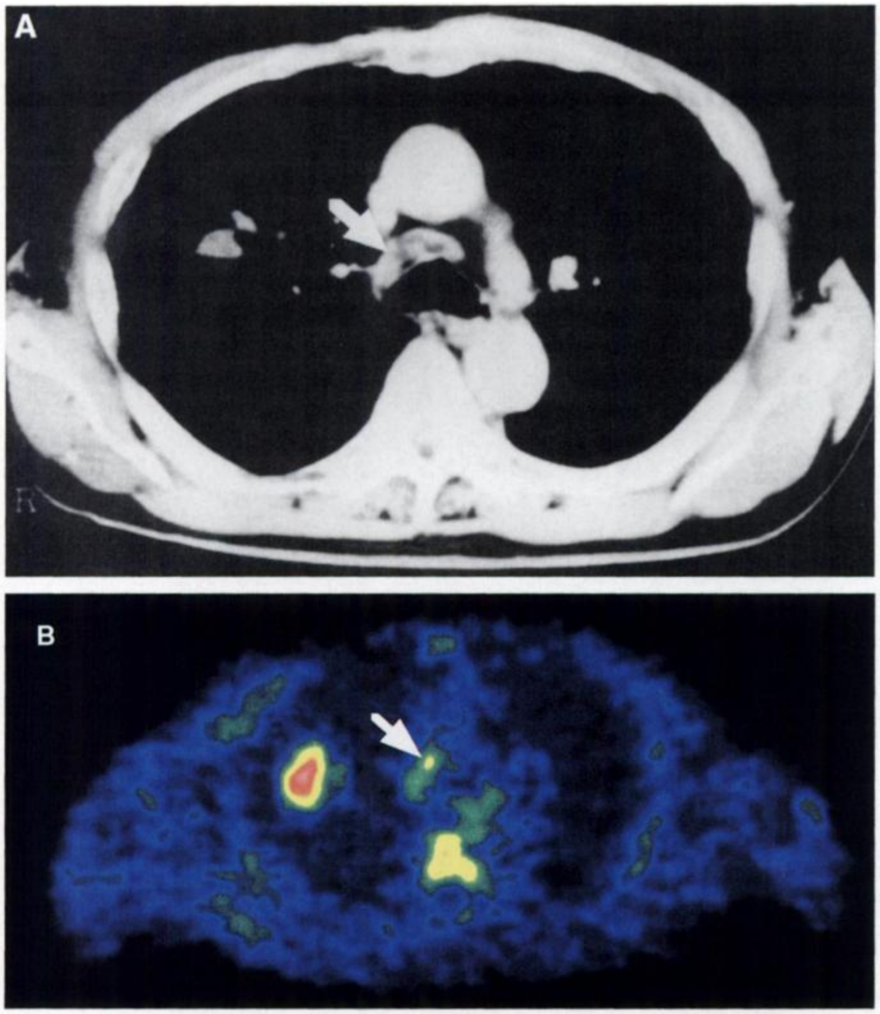

FIGURE 1. (A) CT scan shows lung tumor in right S3 and pretracheal lymph node swelling (>10 mm). (B) Methionine PET image shows very high accumulation in tumor (TMR 4.9) and low accumulation in lymph node (TMR 2.3, histologically negative).

were 79.5% (31/39) and 94.3% (82/87), respectively. The sensitivity, specificity, and accuracy of PET were 86.1% (31/36), 91.1%(82/90), and 89.7% (113/126), respectively (Table 3). The positive and negative predictive value, sensitivity, and accuracy of PET were significantly higher than those of CT (Table 4). The distributions of TMRs for positive and negative lymph nodes are shown in Figures 5 and 6. All positive nodes with short-axis diameters >10 mm, which were diagnosed correctly by CT, and 11 of 13 positive nodes, which were 6–10 mm in short-axis diameter, were correctly diagnosed by PET. However, only 1 of 4 positive nodes with a short-axis diameter <6 mm could be diagnosed by PET (Fig. 5). No false-positive lymph nodes were observed among the small-sized group by PET. Four of 25 medium-sized and 4 of 14 large-sized lymph nodes were falsely diagnosed as positive (Fig. 6). Thus, PET corrected the diagnosis of 10 of 14 lymph nodes that gave false-positive results on CT. In this study, the axial field of the PET devices (108 mm) restricted the diagnosis of N-stage. However, within the limitations of this field, PET diagnosis of N-stage (34/41, 82.9%) was superior to that by CT (28/41, 68.3%). PET corrected the N-stage diagnosis in 7 cases and gave a misleading result in 1 case.

Histological Analysis of Results of PET Analysis

Three of 5 lymph nodes that showed false-negative results in the PET study were included in the small-sized group, and 1 medium-sized lymph node diagnosed as false-negative, for which the TMR was 2.24, had only tiny metastatic cancer foci <1 mm in diameter (Fig. 7).

Six of 8 false-positive lymph nodes had no specific findings on histological analysis. These lymph nodes were relatively large; 2 and 4 belonged to the large- and medium-sized groups, respectively. These lymph nodes showed only sinus histiocytosis, which is commonly seen in the lymph nodes of cancer patients. The remaining 2 histologically negative lymph nodes, for which the TMRs were 5.52 and 4.56, however, were large, with short-axis diameters of 14 and 15 mm, respectively, on CT, and showed multiple follicle formation with infiltration of macrophages or plasma cells in the parafollicular area. These findings were suggestive of nonspecific reactive lymph node swelling associated

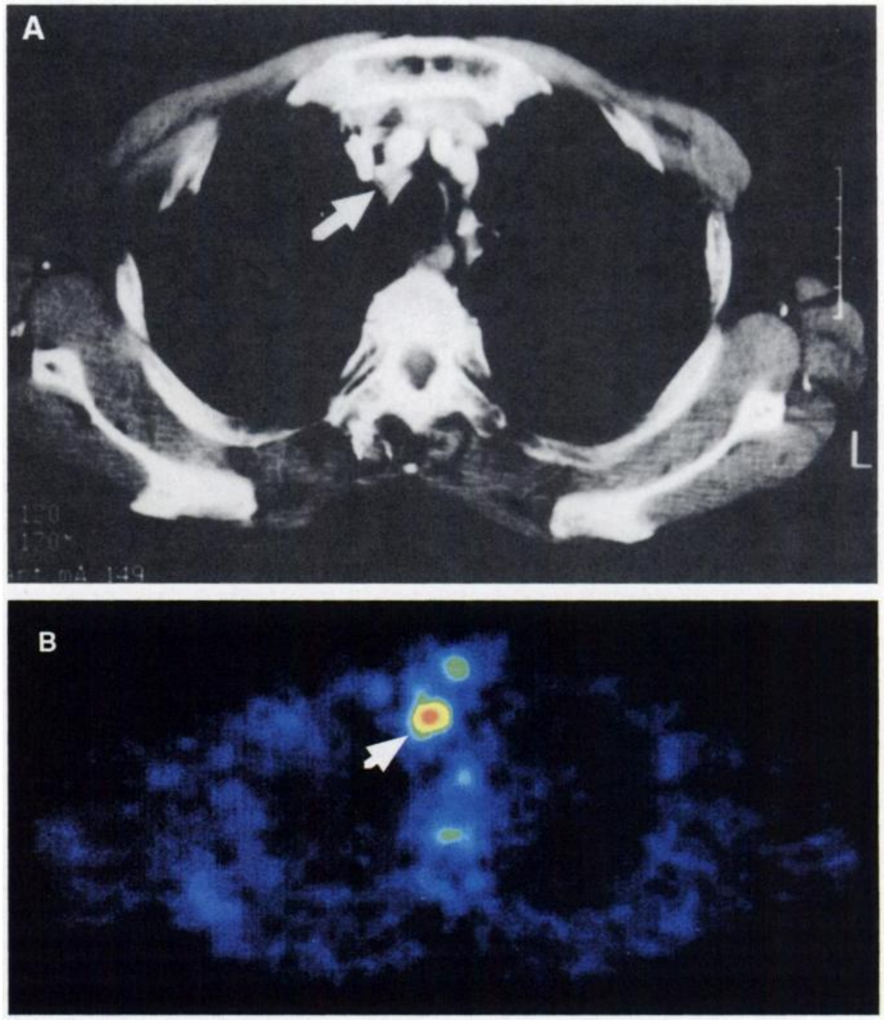

FIGURE 2. (A) CT scan shows highest mediastinal lymph node (8 mm in short-axis diameter). (B) Methionine PET image shows very high accumulation in this lymph node (TMR 6.0, histologically positive).

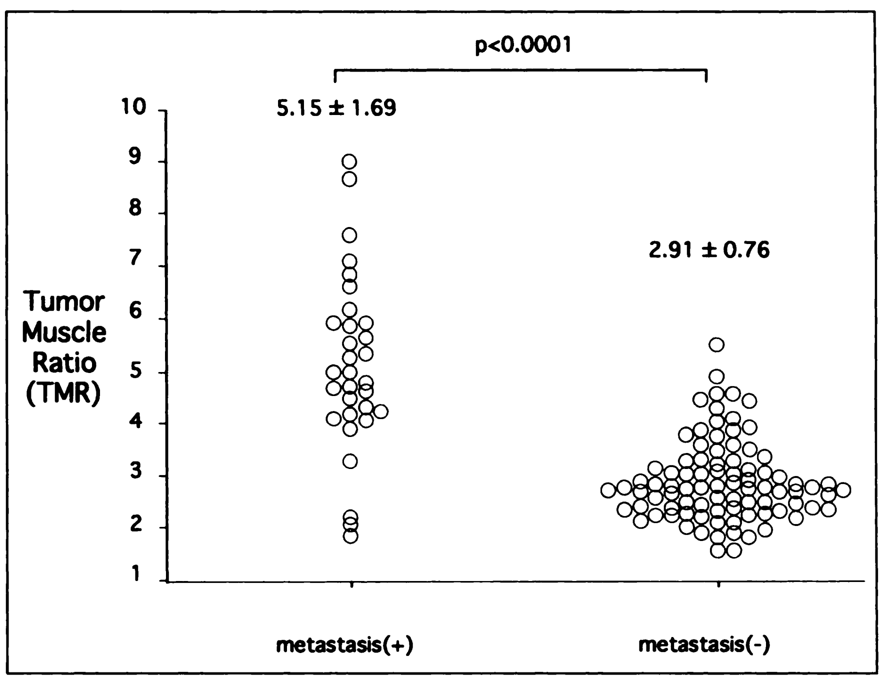

FIGURE 3. TMR of metastatic lymph nodes was significantly higher than that of nonmetastatic lymph nodes ($P < 0.0001$, unpaired t test).

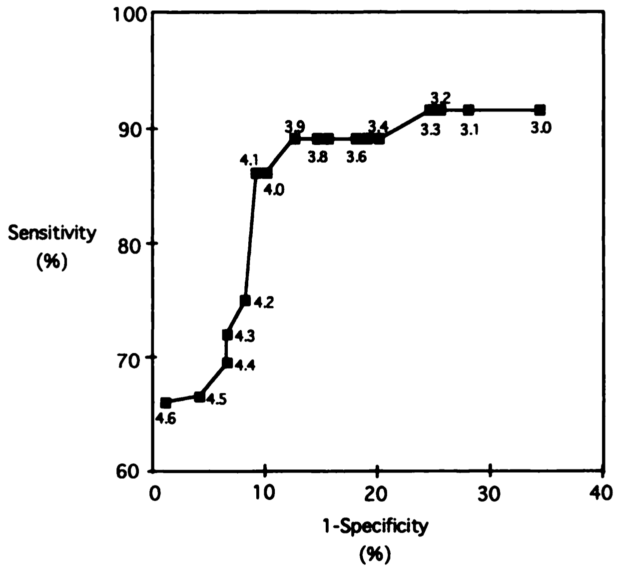

FIGURE 4. TMR cutoff value for diagnosis of lymph node metastasis based on ROC curve analysis was 4.1.

with chronic inflammation such as obstructive pneumonia or chronic bronchitis.

DISCUSSION

To select an appropriate treatment regimen for lung cancer patients, it is of the utmost importance that lymph node metastasis is correctly diagnosed before treatment. Morphological diagnosis by CT based on size criteria is commonly performed for the staging of lymph node lesions in lung cancer patients. However, the sensitivity and specificity of this method are low (*1–3*).

PET can demonstrate increased metabolic demand as visual images and produces alternative information for diagnosis that can be used to complement morphological observations. PET has been widely used to detect and evaluate various malignant diseases, and several studies have indicated its usefulness (*11–15*). FDG PET studies for staging of lymph node lesions in lung cancer patients have also been reported (*4–10*). The sensitivity and specificity of FDG PET were reported to be higher than those of CT. Several studies have indicated the usefulness of methionine PET for the detection of malignant lesions and evaluation of malignant grade (*16*). Kubota et al. (*11*) reported that there were no significant differences in sensitivity or specificity between FDG PET and methionine PET for the differential diagnosis of lung cancer. Inoue et al. (*17*) showed that FDG PET and methionine PET were equally effective in detecting residual or recurrent malignant tumors. This study is the first investigation of the use of methionine PET for detection of hilar and mediastinal lymph node metastases in lung cancer patients. Methionine has been shown to be essential for tumor growth and is necessary for both protein and polyamine synthesis and transmethylation reactions. Cancer cells are dependent on an external methionine supply, whereas normal cells can produce methionine from homocysteine (*18,19*). The concentration of radioactivity because of ^{11}C-methionine increases rapidly in tumors and remains 25–40 min after injection (*20*).

The positive and negative predictive values, sensitivity, and accuracy of methionine PET were superior to those of CT. In particular, the negative predictive value and sensitivity of methionine PET were higher than values of CT (94.3% versus 81.7% and 86.1% versus 52.8%, respectively). Only 19 of 33 lymph nodes belonging to the large-sized group diagnosed as positive in CT showed metastasis. Methionine PET gave accurate diagnoses to 10 of these 14 lymph nodes that had been false-positive on CT. All true-positive lymph nodes on CT (n = 19) were also true-positive on methionine PET, and 12 of 17 lymph nodes false-negative on CT were correctly diagnosed by methionine PET.

Morphological and histological investigation showed that 3 of 5 lymph nodes falsely diagnosed as negative by methionine PET were small (≤5 mm) and the remaining 2 were medium sized (6–10 mm). However, they contained very small cancer foci with long axes of 1–2 mm in pathological measurement. Methionine is taken up by both cancer cells and normal cells, and methionine PET can detect only the difference in uptake level. Therefore, the methionine uptake of small lesions may have been underestimated as a result of the spatial resolution of the PET device (e.g., because of the partial-volume effect). Considering the spatial resolution of our PET device (FWHM, 8 mm),

TABLE 3
Lymph Node Status by PET (TMR Cutoff = 4.1)

Histology	PET* Positive	PET* Negative
Positive, 36	31	5
Negative, 90	8	82

*Positive predictive value, 79.5%; negative predictive value, 94.3%; sensitivity, 86.1%; specificity, 91.1%; accuracy, 89.7%.

TABLE 4
Reliability of PET and CT

Determinants	PET (%)	CT (%)	P*
Positive predictive value	79.5	57.6	0.04
Negative predictive value	94.3	81.7	0.008
Sensitivity	86.1	52.8	0.002
Specificity	91.1	84.4	NS
Accuracy	89.7	75.4	0.002

*McNemar test.
NS = not significant.

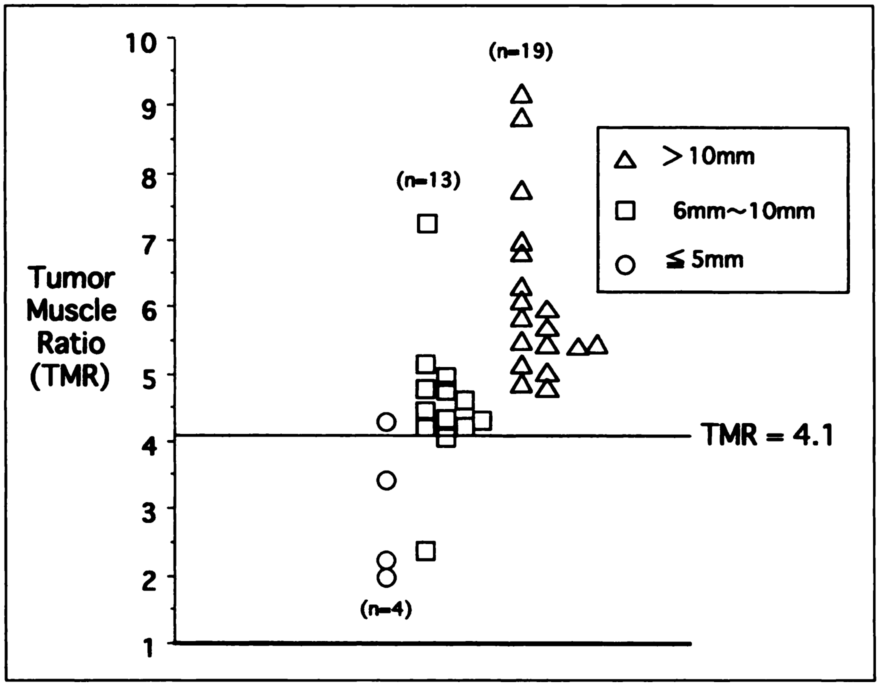

FIGURE 5. Distribution of TMR of histologically positive nodes according to CT classification by size criteria.

artifacts resulting from respiration movement, image reconstruction, biological factors, etc., it would be difficult to evaluate small lesions such as those in lymph nodes with a short-axis diameter <5 mm. Therefore, such lymph nodes should not be examined by methionine PET. However, for those lymph nodes with a short-axis diameter >5 mm on corresponding CT, the sensitivity of methionine PET was excellent (93.8%).

We also investigated false-positive results. Four of 8 lymph nodes were large sized, and the remaining 4 were medium sized. No lymph nodes belonging to the small-size group gave false-positive results. Two large lymph nodes showed swelling as a result of inflammatory processes such as obstructive pneumonia, and the remaining 6 showed nonspecific reactive swelling often observed in lung cancer patients. Kubota et al. (*21*) showed that FDG was highly

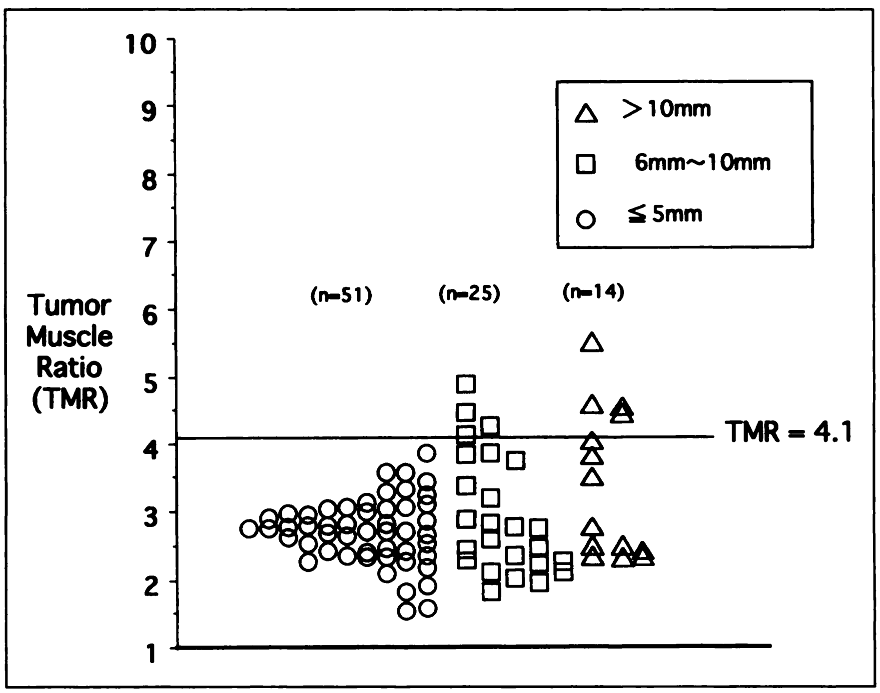

FIGURE 6. Distribution of TMR of histologically negative nodes according to CT classification by size criteria.

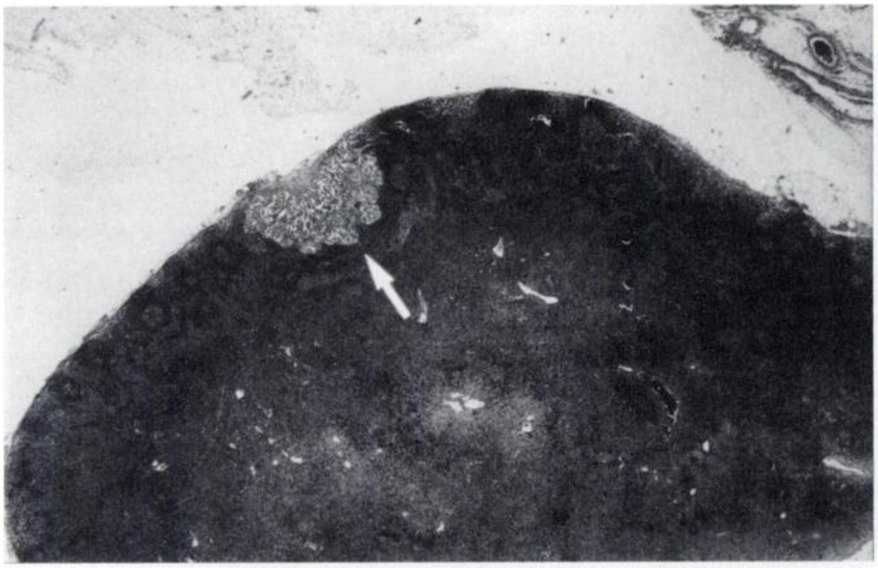

FIGURE 7. Lymph node with short-axis diameter of 8 mm, falsely diagnosed as negative by methionine PET, was shown to have tiny metastatic foci 1–2 mm in diameter (arrow; original magnification, ×3.125).

accumulated not only in tumor cells but also in macrophages and granulation tissues. Therefore, FDG is not very tumor specific, and its accumulation in benign lesions with increased glucose metabolism may yield false-positive results (*22*). Unfortunately, methionine PET yielded similar results, and several lymph nodes showing some degree of enlargement could be falsely diagnosed as positive. However, in contrast to FDG PET, no specific histological findings were observed in false-positive lymph nodes.

These results suggest that lymph node metastasis can be excluded in cases in which CT indicates a lymph node with at least 5 mm in short-axis diameter but in which methionine PET shows no marked accumulation. When no lymph node with a short-axis diameter >5 mm is detected on CT, methionine PET might not provide additional useful information (Table 5).

CONCLUSION

Methionine PET should be used to assess those lymph nodes with a short-axis diameter >5 mm on CT, to obtain more accurate diagnosis of lymph node metastasis in lung cancer patients. More accurate lymph node diagnosis acquired by PET analysis enabled us to select more appropriate treatment regimens for lung cancer patients, particularly for the patient with positive mediastinal lymph nodes on CT, for whom the indication of surgical treatment could be determined without mediastinoscopy. Although a few false-negative nodes were detected in our methionine PET study, the methionine uptake of malignant cells was markedly higher than that of normal cells. Future development of PET devices with a higher resolution may increase the ability to detect lymph node metastasis with methionine PET.

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TABLE 5
Indication and Evaluation of Methionine PET Study

Lymph node size on CT > 5 mm (short-axis diameter)	→ Methionine PET negative		→	Metastasis (−)
	Medium (6–10 mm)	91.3% (31/33)	Total 93.9% (31/33)	
	Large (>10 mm)	100% (10/10)		
	→ Methionine PET positive		→	Metastasis (+) suspect
	Medium (6–10 mm)	73.3% (11/15)	Total 78.9% (30/38)	
	Large (>10 mm)	82.6% (19/23)		
Lymph node size on CT ≤ 5 mm (short-axis diameter)	→		→	Metastasis (−)
	CT		92.7% (51/55)	
	CT + methionine PET		94.5% (52/55)	

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