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Original article

Usefulness of Delayed Scan of FDG PET for the Diagnosis of Lymph Node Metastasis in Non-Small Cell Lung Cancer

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Abstract: PURPOSE: The purpose of this study was to evaluate the usefulness of delayed scan of ^{18}F fluorodeoxyglucose positron emission tomography (FDG-PET) for the diagnosis of lymph node (LN) metastasis in non-small cell lung cancer (NSCLC).
METHODS: The subjects were 92 patients with NSCLC, who were examined dual-time-point FDG-PET. A total of 510 LN stations were evaluated histologically. The maximum standardized uptake values (SUV) of LN stations were measured at early and delayed phases on FDG-PET study. We evaluated the diagnostic accuracy of LN metastasis when using the combined criteria of early SUV and retention index (RI) cut-off value in comparison with that using early SUV alone.
RESULTS: The mean RIs of the LN stations with and without metastasis were 15.67 ± 19.07% and –1.93 ± 14.66% ($p<0.01$). When the cut-off value of SUV at early scan as the criterion of malignancy was set at 2.5 and 2.0, the sensitivities, specificities, and accuracies were 39.3%, 94.3% and 88.2% (SUV>2.5), and 66.1%, 79.5% and 78.0% (SUV>2.0). If RI more than 10% was added into the criteria, the sensitivities, specificities, and accuracies became 32.1%, 98.2% and 91.0% (SUV>2.5), 53.6%, 96.5% and 91.8% (SUV>2.0).
CONCLUSIONS: Metastatic LNs have a higher RI than non-metastatic ones. The combined criteria of early SUV and RI can improve the accuracy of the diagnosis of LN metastasis in NSCLC.

Key Words: FDG PET, lung cancer, lymph node metastasis

INTRODUCTION

NSCLC is important for choosing an appropriate treatment. Computed tomography (CT) is currently being used for this purpose. However, CT has limited value in the evaluation of nodal staging[1]. It has been reported that FDG-PET is a more useful modality for diagnosing the nodal stage of lung cancer than CT[2]. Several studies demonstrated that the sensitivity and specificity ranges of FDG-PET for diagnosing metastatic lymph nodes were 73-100% and 81-100%, respectively[2–5]. However, FDG may also accumulate in benign lymph nodes with reactive hyperplasia or active inflammation due to granulomatous disease such as tuberculosis[6]. Therefore, it is sometimes difficult to differentiate between benign lymph nodes and metastatic lymph nodes with FDG-PET. PET scan is usually started at 60 minutes after the FDG admin-

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istration and is completed with this one scan. In an animal study, however, it was shown that the FDG uptake of malignant tumors constantly increased during 120-180 minutes[7]. Yamada *et al.* documented that the FDG uptake of inflammatory tissue gradually increased until 60 minutes and then decreased[8]. Some human studies have also shown that the delayed FDG-PET scan may be helpful in differentiating between malignant and benign lesions[9–12] based on the fact that FDG uptake in malignant lesions are more likely to increase at delayed phase in contrast with that of benign lesions, which are more likely to decrease or unchanged. Although the usefulness of delayed scan in differentiating between malignancy and benignancy has been investigated in several reports, few focused on the differentiation between metastatic and non-metastatic lymph nodes. In addition, optimal cut-off value of RI when adding a delayed scan is not clarified yet. Thus, the purposes of this study were to determine the optimal cut-off value of RI and to evaluate the diagnostic capability of FDG-PET when adding the delayed scan and using the optimal RI for the evaluation of lymph node metastasis in NSCLC.

MATERIALS AND METHODS

The subjects were the patients who were referred to the institution where this study was conducted for FDG-PET of NSCLC staging from four neighborhood hospitals between May 2005 and November 2006. Delayed phase scan had been routinely included in FDG-PET of all the patients with suspected NSCLC in the institution. Written informed consent was obtained from all patients. Among these patients, 92 patients (63 men and 29 women; mean age, 68.5 ± 8.3 years; range, 49-80 years) who underwent curative surgical resection for lung cancer, including lymph node dissection, were enrolled in this study. Histologic subtypes of the tumors were 59 adenocarcinomas, 27 squamous cell carcinomas, 3 large cell carcinomas, 1 mucoepidermoid carcinoma, 1 pleomorphic carcinoma and 1 adenosquamous carcinoma (clinical tumor stage(T); T1: n=46, T2:n=37, T3:n=7, T4:n=2).

All patients fasted for at least 6 hours before the FDG-PET examination although oral hydration with glucose-free water was allowed. After ensuring that peripheral blood glucose level is lower than 150 mg/dL, patients received an intravenous injection of 3 MBq/kg of FDG. Scans were acquired with a PET/CT device (Biograph DUO LSO; Siemens Medical Solutions, Erlangen, Germany) that consisted of a PET scanner and a two-section CT scanner. The axes of both systems were mechanically aligned so that the patient could be moved from the CT scanner to the PET scanner gantry. Thus the resulting PET and CT scans were coregistered on hardware.

CT was performed with the following settings: 110 kV; 30 mA; tube rotation time, 0.8 second per rotation; pitch, 2; and section thickness, 2.5 mm. Patients maintained normal shallow respiration during the acquisition of CT scans. No iodinated contrast material was administered. Immediately after the CT scans, PET scans were performed in the identical transverse field of view. PET scans were acquired in the three-dimensional mode with a matrix size of 128 × 128. The acquisition time for PET was 2 minutes per table position. The CT data were resized from a 512 × 512 matrix to a 128 × 128 matrix to match the PET data so that the both scans could be fused and CT-based transmission maps could be generated. PET data sets were reconstructed iteratively with an ordered subsets expectation maximization algorithm and segmented attenuation correction (two iterations, 8 subsets) and the CT data. Coregistered scans were displayed

by using a dedicated software (e.soft-PET; Siemens Medical Solutions).

Early scan from the skull base to the pelvic floor was performed at 60 minutes after the injection of FDG, and delayed scan for chest was performed at 120 minutes after the injection. If lymph nodes were visible on PET images, a region of interest (ROI) was placed over the lymph node by using a 3D acquisition. SUV of each mediastinal and hilar lymph nodes station was measured at early and delayed phases. SUV was calculated according to the following formula:

$$SUV = \frac{\text{Tissue activity (MBq/ml)}}{\text{Injected dose (MBq) / Body weight (g)}}$$

For the lymph node stations that showed definite accumulation (defined as SUV of 1.5 or more at early phase), we calculated the retention index (RI (%) =[delayed SUV − early SUV] × 100 / early SUV) of these lymph node stations. RI was described in percentage.

The mean RIs for metastatic and non-metastatic lymph node stations were calculated, and were compared by using Student's t-test. In addition different cut-off values for RI were compared by using receiver-operating-characteristic (ROC) analysis to determine the best value with the highest sum of sensitivity and specificity in diagnosing lymph node metastasis. Finally, we evaluated the diagnostic accuracy of lymph node metastasis when using the combined criteria of early SUV and RI in comparison with that using early SUV alone.

Results

A total of 510 lymph node stations (260 mediastinal lymph node stations and 250 hilar lymph node stations) were evaluated on pathology after the surgical resections. Of these, 56 lymph node stations (19 mediastinal lymph node stations and 37 hilar lymph node stations) in 36 patients (Nodal stage(N); N0: n=56, N1:n=21, N2:n=15) proved to be positive for metastasis.

273 lymph node stations showed definite accumulation on early FDG-PET scan (SUV of 1.5 or more at early phase), of which 47 lymph node stations (16 mediastinal lymph node stations and 31 hilar lymph node stations) were positive for metastasis. The mean RIs of the lymph node stations with and without metastasis were 15.67 ± 19.07 (n=47), –1.93 ± 14.66 (n=226), respectively; the mean RIs of the me-

Table 1. The mean RIs of the lymph node stations with metastasis and without metastasis

	With metastasis	Without metastasis	P value*
Mediastinal	15.95±16.99 (n=16)	-1.80±13.68 (n=125)	P<0.01
Hilar	15.52±20.33 (n=31)	-2.08±14.34 (n=101)	P<0.01
Total	15.67±19.07 (n=47)	-1.93±14.66 (n=226)	P<0.01

* Student's t-test.

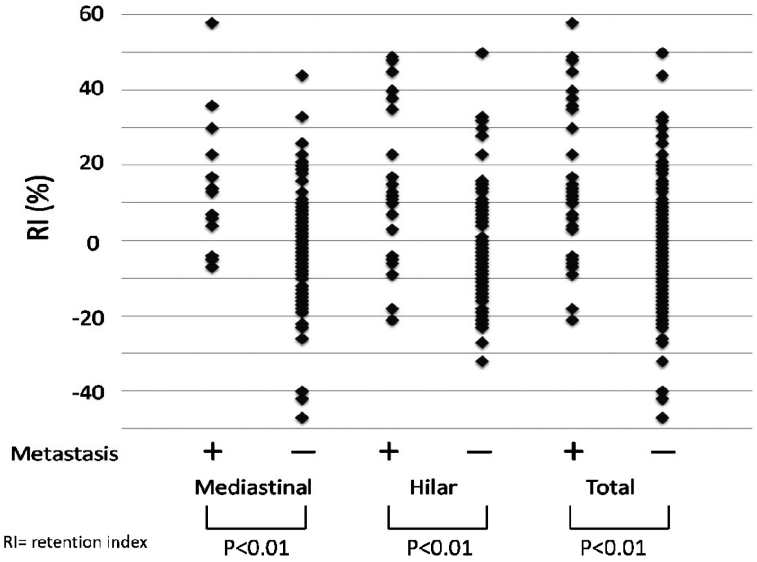

Fig. 1. Scattergram of RI in the lymph node stations with and without metastasis. The RI ranges considerably overlap between metastatic and non-metastatic lymph node stations.

diastinal lymph node with and without metastasis were 15.95±16.99 (n=16), –1.80±13.68 (n=125), and those of the hilar lymph node were 15.52±20.33 (n=31), –2.08±14.34 (n=101), respectively (Table 1). There were statistically significant differences ($p<0.01$) between these mean RIs with and without metastasis. However, the RI ranges considerably overlapped between metastatic and non-metastatic lymph node stations in the scatter gram (Fig. 1)

Various cut-off values of RI were replicated by ROC analysis to estimate the best value that showed the highest sum of sensitivity and specificity in diagnosing lymph node metastasis (Fig. 2). When the cut-off value of RI was 10%, the highest sum of sensitivity and specificity was obtained (sensitivity 68.1%, specificity 84.1%). The diagnostic accuracies of lymph node metastasis when using other cut-off RIs are summarized in Table 2.

When the cut-off value of SUV obtained at early scan as the criterion of metastasis was set at 2.5 or 2.0, the sensitivities (we defined that SUV>2.5(2.0) was metastasis, SUV≦2.5(2.0)

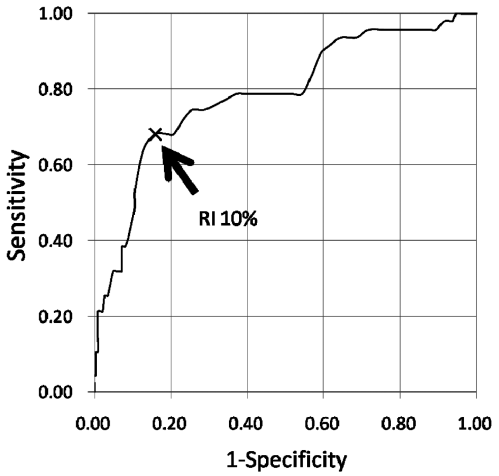

Fig. 2. ROC curve of diagnosing lymph node metastasis with RI thresholds. When RI threshold is set at 10%, the highest sum of sensitivity and specificity is obtained (sensitivity 68.1%, specificity 83.6%).

Table 2. Performance of diagnosing lymph node metastasis with RI as estimated by ROC analysis

RI	>0%	>5%	>10%	>15%	>20%	>25%
Sensitivity	78.7% (37/47)	74.5% (35/47)	68.1% (32/47)	40.4% (19/47)	31.9% (15/47)	25.5% (12/47)
Specificity	53.1% (120/226)	71.2% (161/226)	84.1% (190/226)	91.2% (206/226)	93.8% (212/226)	96.5% (218/226)
Sensitivity + Specificity	131.8%	145.7%	152.2%	131.6%	125.7%	122.0%

Table 3. Comparison of diagnostic capability of lymph node metastasis between early SUV alone and combined early SUV and RI

Cut-off value	Sensitivity	Specificity	Accuracy	
SUV>2.5	39.3% (22/56)	94.3% (428/454)	88.2% (450/510)	P<0.05
SUV>2.0	66.1% (37/56)	79.5% (361/454)	78.0% (398/510)	
SUV>2.5 and RI>10%	32.1% (18/56)	98.2% (446/454)	91.0% (460/510)	P<0.05
SUV>2.0 and RI>10%	53.6% (30/56)	96.5% (438/454)	91.8% (468/510)	

*χ^2-test

was non-metastasis.), specificities and accuracies became 39.3%, 94.3% and 88.2% (SUV>2.5), 66.1%, 79.5% and 78.0% (SUV>2.0), respectively. If the RI criterion of 10% was added into the criterion (we defined that SUV>2.5(2.0) and RI>10% was metastasis, SUV≦2.5(2.0) or RI≦10% were non-metastasis.), the sensitivities, specificities and accuracies became 32.1%, 98.2% and 91.0% (SUV>2.5), 53.6%, 96.5% and 91.8% (SUV>2.0), respectively (Table 3). The combined criteria of early SUV and RI improved the accuracy of the diagnosis of lymph node metastasis in comparison with early SUV alone. In addition, the combined criterion of SUV>2.0 and RI>10% was higher accuracy than the criteria with early SUV alone (SUV>2.5, SUV>2.0), significantly ($p<0.05$).

Discussion

FDG-PET is currently considered to be the most reliable imaging method for the nodal staging of lung cancer. It has been reported that FDG-PET is a more useful modality for diagnosing the nodal stage of lung cancer than CT[2]. However, FDG has been reported to also accumulate in benign lymph nodes involved by granulomatous disease, producing false-positive results[13]. It is believed that abundant histiocytes in the lymph nodes result in increased accumulation of FDG. In Japan, as tuberculosis is endemic, many patients have enlarged lymph nodes in the mediastinum and pulmonary hilus due to old tuberculosis[14]. These lymph nodes cause false positive findings on FDG-PET as well

as on CT[15]. Consequently, a substantial overlap between the SUVs of metastatic and non-metastatic lymph nodes results. Therefore, some modification in the examination is required to improve the diagnostic accuracy.

Delayed FDG-PET scan (dual-time-point FDG-PET scan) has been proposed to solve this problem and to achieve a better diagnostic accuracy[9–12]. Matthies *et al.* studied 36 patients with pulmonary nodules using dual-time-point FDG-PET. There were 38 lesions, consisting of 20 malignant nodules verified by pathological examination and 18 benign nodules. All malignant nodules showed an increase of SUV on delayed images, while only six of the benign nodules showed an increase in SUV and the remaining 12 showed no increase in SUV on delayed images[12]. Ma *et al.*[16] reported that a delayed image at 180 minutes is helpful for detecting paraaortic lymph node metastasis of uterine cervical cancer patients because of the increased accumulation in metastatic lymph nodes in comparison with decreased normal background. In their study, the mean RI in metastatic lymph nodes was significantly higher than those in non-metastatic lymph nodes.

We documented that mean RI of metastatic lymph nodes was higher than that of non-metastatic lymph nodes in NSCLC patients. This result was concordant well with the results of the previous reports that investigated the RI on FDG-PET in other malignancies. Moreover, our results demonstrated that combined criteria of early SUV and RI can improve the diagnostic accuracy of nodal staging in NSCLC. The RI criterion prevents non-metastatic lymph nodes with avid accumulation at early scan from being judged as metastatic by the absence of retention of FDG. Thus, the number of false positive decreases and accuracy increases. However, the sensitivities of the combined criteria were mildly decreased in comparison with those of early SUV alone. This result indicates that some metastatic lymph nodes did not increase SUV at delayed scan. We should note that addition of delayed scan may decrease sensitivity in nodal staging. However, from the practical point of view, specificity may be preferred to sensitivity because false positive lymph nodes potentially preclude lung cancer patients from a chance to undergo a curative treatment, such as surgery. In the cases suspected two or more metastatic mediastinal lymph node stations preoperatively, it comes in predisposed to avoid operation. If we use this diagnostic criteria to bring the high specificity, false positive is small, it is possible to determine the surgery avoidance cased with high confidence.

The cut-off values of RI and early SUV to differentiate between benignancy and malignancy remains controversial. Generally, RI of 0% in dual-time-point FDG-PET scan has been used as the cut-off value for evaluating malignant lesions[9, 17]. However, in other studies, 10% increase criterion for distinguishing malignant lesions from benign ones[12, 18, 19] was used. Lan *et al.*[19] reported that pulmonary malignant tumors had the mean RI of 32%, whereas that of benign tumors was approximately –1%. In their study, it seems likely that 10% was more suitable than 0% as the cut-off value of RI. If RI threshold was set at 0%, an unacceptable false-positive rate must have resulted. We found that RI of 10% or more showed the highest sum of sensitivity and specificity in differentiating between metastatic and non-metastatic lymph nodes by ROC analysis. When RI of more than 0% was used as the cut-off value, specificity considerably fell as in the report by Lan, *et al.*[18] We suggest 10% as the cut-off value of RI when diagnosing nodal stage in NSCLC.

The cut-off value of early SUV for distinguish-

ing malignant lesions from benign ones is also controversial. In general, as the cut-off value of early SUV increases, sensitivity decreases and specificity increases. Hellwig *et al.*[20] reported that when the SUV of more than 2.5 as the threshold for staging mediastinal lymph nodes in lung cancer was chosen, the sum of false-negative rate and false-positive rate was minimized. However, when we selected a SUV threshold of 2.5 in single-point scan (early scan alone), the sensitivity was quite low (39.3%) in our series. When the cut-off value of SUV was lowered to 2.0, sensitivity was improved but false positive increased. Therefore, we added 10% RI as a criterion of lymph node metastasis to the cut-off value of SUV (2.0) and thereby a high accuracy without compromising sensitivity and specificity was achieved.

There are limitations in our study. First, the sensitivities in our study were generally much lower than those of the previous studies. Microscopic metastasis is considered as the major reason of these results. In fact, some metastatic foci in the lymph nodes were too small to be detected by FDG-PET or CT in this study. Accumulation of FDG in small metastatic foci is often underestimated on FDG-PET due to partial volume effect or motion artifacts caused by respiratory movement or cardiac pulsation. Second, RI was calculated only when lymph node stations had clear accumulation because of difficulty in placing region of interest on small lymph nodes. Therefore, a sizable number of the lymph node stations, including those containing metastatic lymph nodes, were not evaluated in this study. Third, as our subjects were the patients who underwent a curative thoracic surgery, it is uncertain that our results could be applied to lung cancer patients with more advanced stage (e.g. N3). However, the pattern of FDG accumulation is not related to the location of lymph nodes and therefore we think that our results will be also valid in advanced disease. Finally, our modifications in the criteria for nodal staging were retrospective and might have been biased. Further study will be needed to definitely conclude that our criteria are optimal for nodal staging in NSCLC.

Conclusion

The results of this study suggest that RI cut-off value of 10% is most appropriate for the differentiation between metastatic and non-metastatic lymph nodes in NSCLC. In addition, the combined criteria of early SUV and this RI can improve the accuracy of the diagnosis of lymph node metastasis in NSCLC. Therefore, addition of delayed scan is recommended in FDG-PET of staging in NSCLC.

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