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High correlations between primary tumours and loco-regional metastatic lymph nodes in non-small-cell lung cancer with respect to glucose transporter type 1-mediated 2-deoxy-2-F18-fluoro-D-glucose uptake

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ABSTRACT

The purpose of the study was to investigate whether glucose transporter type 1 (Glut-1) mediated 2-deoxy-2-F18-fluoro-D-glucose (FDG) uptake of primary tumour is related to the likelihood of malignancy involvement in loco-regional lymph nodes (LNs) in 126 non-small-cell lung cancer (NSCLC) patients (M:F = 103:23, age = 65 ± 9.7 years). Maximum standardised uptake values (maxSUV) and Glut-1 expression levels (determined by PET and immunostaining, respectively) of primary tumours and PET positive loco-regional LNs were compared. Significant correlations were found between malignant LNs and primary tumours with respect to maxSUV ($r = 0.6451$, $p < 0.0001$), %Glut-1 expression ($r = 0.8341$, $p < 0.0001$) and Glut-1 staining intensity ($\rho = 0.827$, $p < 0.0001$). The area-under-curve value for LN differentiation using lymph node maxSUV was significantly higher in patients with a primary tumour maxSUV of >6 (AUC = 0.775, $p = 0.0001$). High correlations between the primary tumours and metastatic LNs in NSCLC with respect to the Glut-1 mediated FDG uptake may be useful for mediastinal LN discrimination by FDG-PET.

1. Introduction

Positron emission tomography (PET) using 2-deoxy-2-F18-fluoro-D-glucose (FDG) has been reported to be valuable for diagnosing loco-regional metastatic lymph nodes in non-small-cell lung cancer (NSCLC) due to high FDG uptake by metastatic lymph nodes.[1,2] FDG uptake in primary NSCLC tumours may reflect major glucose metabolic changes mediated by

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glucose transporter type 1 (Glut-1).[3–5] Furthermore, it has been reported that FDG uptake levels are correlated with tumour aggressiveness[6] and patient survival.[7–11] Moreover, elevated FDG uptake by primary tumours has been suggested to reflect the likelihood of malignancy involvement in loco-regional lymph nodes.[12,13] However, no relation has been reported between primary tumours and loco-regional lymph nodes with respect to FDG uptake and Glut-1 expression. FDG is not a tumour-specific substance, for example, benign lymph nodes with an elevated glucose metabolism may accumulate FDG and produce false-positive results.[14] Thus, a proper understanding of the relations between the metabolic activities of primary tumours and loco-regional metastatic/benign lymph nodes might be useful for lymph node discrimination. Therefore, we investigated correlations between primary tumours and loco-regional lymph nodes in NSCLC with respect to FDG uptake and Glut-1 expression.

2. Methods

2.1. Patients

One hundred and twenty-six consecutive NSCLC patients who underwent primary lung cancer resection and loco-regional lymph node dissection from August 2003 to July 2006 were enrolled. Fifty-three of these patients (42% = 53/126) were included in our previous report.[15] The present study represents an extension of our investigational series regarding lung cancer and FDG-PET.[11,15–17] Surgical resections were performed at most 4 weeks after FDG-PET studies. Exclusion criteria were a neo-adjuvant chemotherapy history, or a true negative PET (PET negative for mediastinal lymph nodes and pathological N0 stage). One hundred and ninety-six PET positive loco-regional lymph nodes (52 malignant and 144 benign) were analysed. All patients provided informed consent concerning the handling of their specimens.

2.2. PET scan

FDG-PET was performed using a dedicated scanner (Allegro, Philips Medical Systems, Cleveland, OH). All patients were fasted for at least 6 h before FDG-PET whole-body scanning. Mean serum glucose level, measured before FDG injection, was 94.3 ± 14.1 mg/dl. F-18 FDG was intravenously injected at 5.18 MBq/kg (0.14 mCi/kg), and whole-body scanning was performed at 50 min after FDG administration from skull base to upper thigh. The 3D row-action maximum-likelihood algorithm was used for image reconstruction, and reconstructed trans-axial images had a resolution of 4.8 mm.

Standardised uptake values (SUVs) were calculated using: SUV = radioactivity in ROI (Bq/ml) × lean body mass (kg)/injected radioactivity (Bq). Lean body masses were used for SUV normalisation to exclude the influence of fatty tissues, which are resistant to FDG uptake,[18] and were calculated using the formula[19]: $1.1 \times \text{weight (kg)} - [128 \times [\text{weight}^2/(100 \times \text{height (m)})^2]]$ for men, and $1.07 \times \text{weight (kg)} - [148 \times [\text{weight}^2/(100 \times \text{height (m)})^2]]$ for women. Circular region of interests (ROIs) were drawn over primary tumours and loco-regional lymph nodes on trans-axial images slice-by-slice repetitively to cover whole lesion volumes. Maximum SUV (maxSUV) was considered to be the representative of FDG uptake.

2.3. Lymph node mapping

Primary tumours and loco-regional lymph nodes were localised using CT and emission PET images. Abnormal FDG uptakes at loco-regional lymph node stations were recorded on lymph node maps in accord with the American Thoracic Society lymph node classification system.[20] The same maps were used for intra-operative staging. Furthermore, the sites of these surgically sampled lymph nodes were recorded on pathology reports using the same maps used for PET readings. Lymph nodes with higher FDG uptake than the adjacent mediastinal blood pool by visual assessment were considered PET positive. PET negative lymph nodes were excluded from the study.

2.4. Glut-1 immunostaining

The Glut-1 immunostaining procedure used has been described in the literature.[11,15] Formalin-fixed, paraffin-embedded 4 μm tissue sections were immunostained with rabbit anti-Glut-1 polyclonal antibody for Glut-1 (1:50, Neomarkers). Sections were dried at 64 °C for 30 min, de-paraffinised in xylene, and re-hydrated in a graded ethanol series. To expose antigens, sections were microwaved in 10 mmol/L sodium citrate buffer (pH 6.0) for 15 min, cooled for 30 min, washed with distilled water for 5 min and then treated with 0.3% hydrogen peroxide in methanol to block endogenous peroxidase activity. After washing with phosphate-buffered saline (PBS, pH 7.4) containing 0.1% polyoxyethylene sorbitan monolaurate (Tween 20), sections were incubated with primary antibody at 37 °C for 60 min, washed with PBS, incubated with biotinylated secondary antibody and streptavidin–biotin–peroxidase complex (LSAB kit; Dako), rewashed in PBS, treated with 3,3′-diaminobenzidine as chromogen, and finally counterstained with haematoxylin.

2.5. Evaluation of histopathology and Glut-1 immunostaining

Histopathology and Glut-1 immunostaining results were evaluated as previously described[11,15] by a pathologist unaware of clinical information. Greatest diameters of primary tumours (cm) and lymph nodes (mm) were measured. %Glut-1 expression was defined as the Glut-1 positive tumour cell proportion (%) within the tumour involved area for primary tumours and malignant lymph nodes, or as the Glut-1 positive follicular centre cell proportion (%) for benign lymph nodes. Glut-1 staining intensities were graded as follows: 1, weak; 2, weak to medium; 3, medium; and 4, intense. Red blood cells in the same slide were used as positive controls for Glut-1 expression. Adjacent sections that had been incubated with rabbit IgG were used as negative controls.

2.6. Statistical analysis

Statistical analysis was performed using MedCalc software (version 9.2.0.2). Correlations between primary tumours and

loco-regional lymph nodes with respect to maxSUV, %Glut-1 expression and greatest diameters were determined by Pearson analysis, whereas the correlation between primary tumours and loco-regional lymph nodes with respect to Glut-1 staining intensity was evaluated by Spearman analysis. Group comparisons of greatest diameters and maxSUVs were conducted using the *t*-test or the Mann–Whitney test. The diagnostic accuracy of lymph node maxSUV was evaluated by receiver-operating-characteristics curve analysis. *p* values of less than 0.05 were considered significant.

3. Results

3.1. *Patient characteristics*

Of the 126 patients, 35 patients had pathologic stage I, 33 stage II, 54 stage III and 4 stage IV NSCLC. The characteristics of the 126 patients are summarised in Table 1. There were 196 PET-positive loco-regional lymph nodes, and of these, 52 were confirmed to be malignant and 144 to be benign based on pathology findings (59.7% = 86/144) or PET/CT image-based clinical follow up with a mean follow up duration of 7.8 ± 3.9 months (ranged 2–16 months) (40.3% = 58/144). MaxSUVs of pathologically proven benign lymph nodes (2.82 ± 0.90) were no different from those of clinically determined benign lymph nodes (2.78 ± 0.69) ($p > 0.05$).

3.2. *Correlations between primary tumours and metastatic lymph nodes with respect to FDG uptake and Glut-1 expression*

Fifty-two lymph nodes in 37 patients were pathologically confirmed as being malignant. Mean lymph node maxSUV was 3.7 ± 2.1 (ranged 1.6–11.5), and mean corresponding primary tumour maxSUV was 6.4 ± 2.9 (ranged 1.0–15.2). A significant correlation was found between the maxSUVs of primary tumours and malignant lymph nodes (Pearson's correlation coefficient $r = 0.6451$; 95% confidence interval 0.4517–0.7806; $p < 0.0001$). Linear regression of the maxSUVs of malignant lymph nodes (Y_1) versus those of primary tumours (X_1) yielded the equation $Y_1 = 0.5938 + 0.4808X_1$ with an r^2 value of 0.4162 (Fig. 1). There were more than 1 FDG positive malignant lymph nodes in 37 patients. A significant correlation was also found between the maxSUVs of primary tumours and the highest maxSUV lymph nodes in the 37 patients ($r = 0.6663$; 95% confidence interval 0.4365–0.8145; $p < 0.0001$).

Forty-eight malignant lymph nodes in 34 patients were immunostained for Glut-1. %Glut-1 expressions of lymph nodes with visualised FDG uptake were found to be significantly correlated with the %Glut-1 expressions of primary tumours ($r = 0.8341$; 95% confidence interval 0.7207–0.9040; $p < 0.0001$). Linear regression of the %Glut-1 expressions of malignant lymph nodes (Y_2) versus those of primary tumours (X_2) yielded the equation $Y_2 = 14.4062 + 0.8673X_2$ ($r^2 = 0.6957$) (Fig. 2). The Glut-1 staining intensities of primary tumours and malignant lymph nodes were also found to be significantly correlated ($\rho = 0.827$; 95% confidence interval 0.664–0.915; $p < 0.0001$).

Mean greatest diameters of primary tumours and malignant lymph nodes were 4.3 ± 2.1 cm and 14.7 ± 6.4 mm, respectively. However, no significant correlation was found between primary tumours and malignant lymph nodes with respect to greatest diameter ($r = 0.1364$, $p = 0.3502$).

3.3. *Correlations between primary tumours and benign lymph nodes with respect to FDG uptake and Glut-1 expression*

FDG uptake was visualised in 144 benign lymph nodes in 75 patients, and their mean lymph node maxSUV was 2.8 ± 0.8 (ranged 1.4–6.6), whereas the mean maxSUV of the corresponding primary tumours was 6.7 ± 3.7 (ranged 1.0–19.9). No relation was found between the maxSUVs of primary tumours and benign lymph nodes ($r = -0.0125$, $p = 0.8831$). Linear regression of the maxSUVs of benign lymph nodes (Y_1) and primary tumours (X_1) yielded the equation $Y_1 = 2.8052 + (-)0.0028X_1$ ($r^2 = 0.0002$) (Fig. 3).

Table 1 – Patient characteristics (n = 126)

Characteristics	No. of patients	%
Sex		
Male	103	81.7
Female	23	18.3
Tumor-cell type		
Adenocarcinoma	72	57.1
Squamous cell carcinoma	42	33.3
Large cell carcinoma	9	7.1
Adenosquamous cell carcinoma	2	1.6
Carcinosarcoma	1	0.8
Pathologic lymph node stage		
N0	45	35.7
N1	32	25.4
N2	48	38.1
N3	1	0.8
Pathologic T stage		
T1	38	30.2
T2	67	53.2
T3	10	7.9
T4	11	8.7

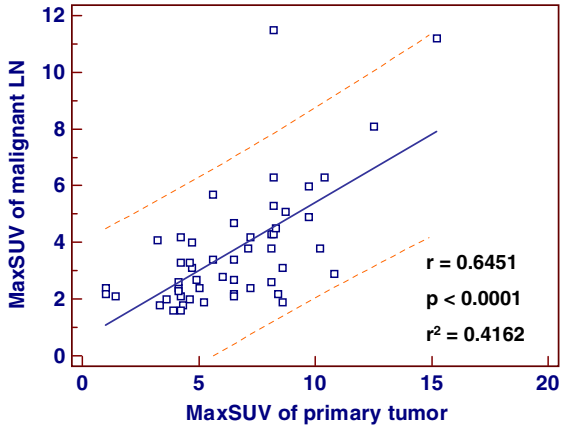

Fig. 1 – Scatter plot of the maxSUVs of primary tumours versus those of malignant lymph nodes, showing the regression line and 95% prediction ranges.

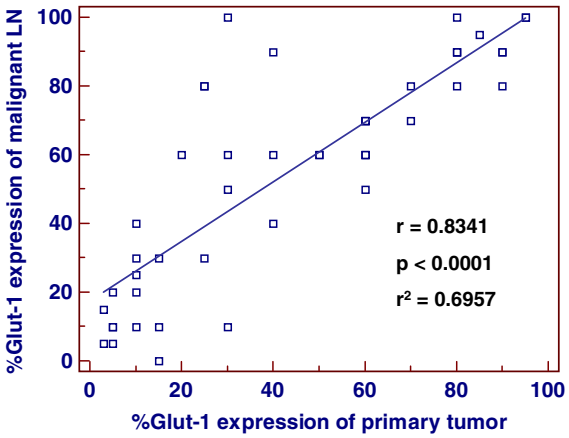

Fig. 2 – Scatter plot of the %Glut-1 expressions of primary tumours versus those of malignant lymph nodes and the associated regression line.

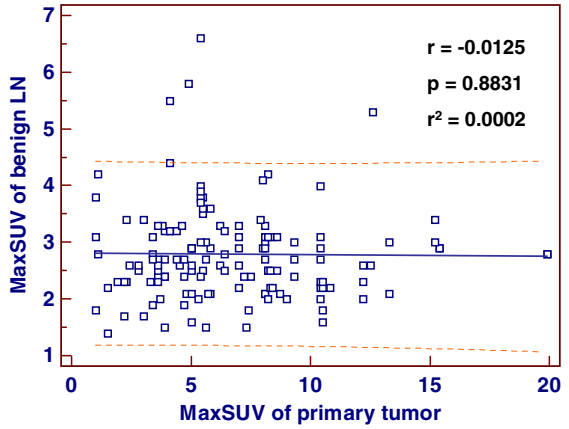

Fig. 3 – Scatter plot of the maxSUVs of primary tumours versus those of benign lymph nodes, showing the regression line and 95% prediction ranges.

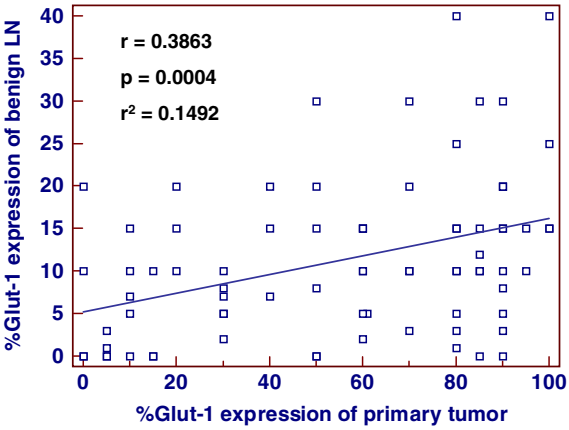

Fig. 4 – Scatter plot of the %Glut-1 expressions of primary tumours versus those of benign lymph nodes and the associated regression line.

Seventy-nine benign lymph nodes in 57 patients were immunostained for Glut-1. Analysis revealed a correlation between the %Glut-1 expressions of primary tumours and benign lymph nodes ($r = 0.3863$, $p = 0.0004$) with a 95% confidence interval range of 0.1806–0.5596. Linear regression of the %Glut-1 expressions of benign lymph nodes (Y_2) versus those of primary tumours (X_2) yielded the equation $Y_2 = 5.1752 + 0.1101X_2$ ($r^2 = 0.1492$) (Fig. 4). However, the Glut-1 staining intensities of primary tumours and benign lymph nodes were not found to be correlated ($\rho = 0.089$; 95% confidence interval –0.183 to 0.348; $p = 0.5179$).

Mean greatest diameters of primary tumours and benign lymph nodes were 3.7 ± 1.9 cm and 11.6 ± 4.7 mm, respectively. No significant correlation was found between the greatest diameters of primary tumours and benign lymph nodes ($r = 0.1403$, $p = 0.1949$).

3.4. *Clinical application of the relation between the maxSUVs of primary tumours and lymph nodes*

Relations between the maxSUVs of malignant and benign lymph nodes and those of primary tumours are presented in Fig. 5. The scatter plot was generated by overlapping Figs. 1 and 3. Substantial overlap was observed between the maxSUVs of malignant and benign lymph nodes, particularly when the maxSUVs of primary tumours were <6 (upper left and lower left parts of Fig. 5). Malignant and benign lymph nodes could be readily discriminated when the primary tumour had a maxSUV >6 (upper right and lower right parts of Fig. 5). Lymph node maxSUV played a crucial role in lymph node discrimination only when the primary tumour maxSUV was >6 with area-under-curve value of 0.775 ($p = 0.0001$) (Fig. 6A). No difference between the greatest diameters of malignant (14.9 ± 5.1 mm) and benign (12.7 ± 4.1 mm) lymph nodes ($p = 0.3401$) was observed when primary tumours had a maxSUV of >6.

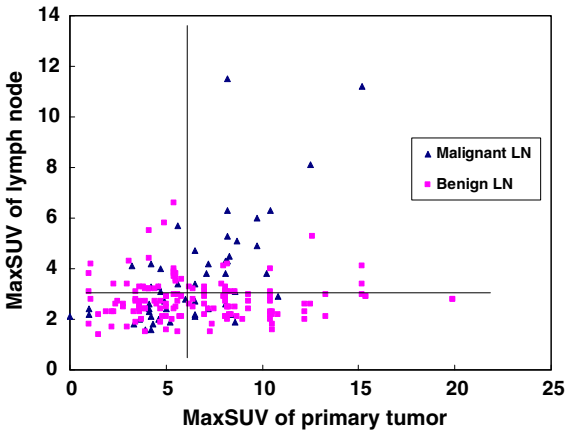

Fig. 5 – Scatter plot of the maxSUVs of primary tumours versus those of malignant and benign lymph nodes. The plot contains a vertical discriminating line for primary tumours at a maxSUV of 6 and a horizontal discriminating line for lymph nodes at a maxSUV of 3.

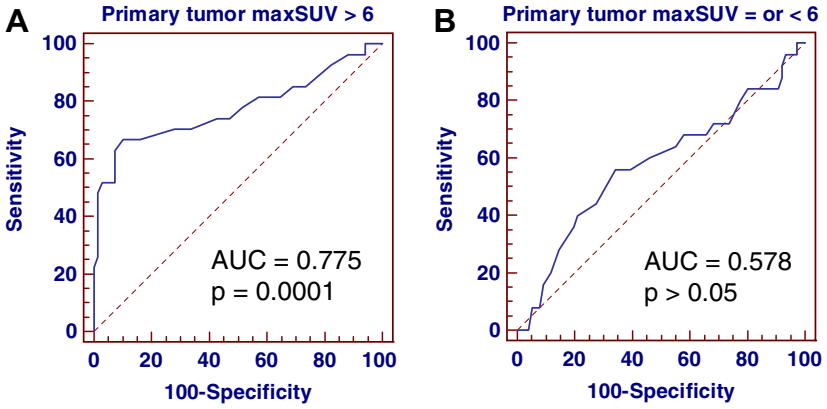

Fig. 6 – Receive-operating-characteristic curve analyses for lymph node discrimination using lymph node maxSUV. When primary tumour maxSUVs were >6, malignant and benign lymph nodes could be readily discriminated (A). However, when primary tumour maxSUVs were ⩽6, malignant and benign lymph nodes could not be differentiated (B).

On the other hand, lymph node maxSUV did not allow malignant and benign lymph nodes to be discriminated when primary tumour maxSUVs were ⩽6 (Fig. 6B).

4. Discussion

The principal finding of the present study is that primary tumours and loco-regional metastatic lymph nodes in NSCLC are highly correlated in terms of their FDG uptakes and Glut-1 expressions, but that no significant relation exists between the FDG uptakes of primary tumours and loco-regional benign lymph nodes. Furthermore, it has been suggested that the Glut expression profiles of primary NSCLC tumours differ from those of metastatic lesions.[21] Therefore, the present study is the first to demonstrate a correlation between the Glut-1 expressions of primary tumours and their metastatic lesions in NSCLC.

Although FDG uptake levels in primary tumours affect the likelihood of metastasis to lymph nodes,[12] and despite the causal relationship reported between FDG uptake and Glut-1 expression in primary tumours[3] and in lymph nodes,[14] the nature of the relationships between primary tumours and loco-regional lymph nodes with respect to their FDG uptakes and Glut-1 expressions are not known. The present study shows that a significant correlation exists between the FDG uptakes of primary tumours and loco-regional metastatic lymph nodes, and in particular, that metastatic lymph node maxSUV values are almost half those of the corresponding primary tumours (Fig. 1), whilst Glut-1 expressions in primary tumours were found to be significantly correlated with those in loco-regional metastatic lymph nodes (Fig. 2). These findings suggest that primary tumours are linked with loco-regional metastatic lymph nodes, but not with benign lymph nodes in terms of glucose metabolic activity.

FDG-PET has been demonstrated to be a powerful tool for detecting loco-regional metastatic lymph nodes in lung cancer,[1,2] and many investigators have attempted to improve the diagnostic accuracy of FDG-PET for mediastinal lymph node staging. Malignant lymph nodes have been classified based on FDG uptake intensities equal to or greater than that of the mediastinal blood pool,[1,22] and a semi-quantitative parameter of FDG uptake (as represented by SUV) was found to be capable of differentiating mediastinal lymph nodes.[23,24] However, due to the small sizes of lymph nodes and partial volume effect, maxSUV has been advocated to overcome the relatively low resolutions of current PET systems,[5,25] and although this method involves representing a tumour by a single pixel, maxSUV can be reliably obtained with little measurement variation.[13,26] In the present study, the mean maxSUV of malignant lymph nodes was half of that of primary tumours, which is in-line with a recent report that suggested that a lymph node/primary tumour maxSUV ratio of 0.58 (ranged 0.32–1.61) could be used to predict the presence of metastatic lymph nodes in NSCLC.[13] However, in this previous study, benign lymph nodes were found to have a maxSUV lymph node/primary tumour ratio of 0.40 (ranged 0.21–1.10), and the overlapping of the maxSUV ratios of malignant and benign lymph nodes resulted in non-impressive AUC values by ROC analysis (ranged 0.40–0.57).[13] We consider that lymph node maxSUV is probably only of use when primary tumour maxSUV is high (Fig. 6A), and that basal FDG uptake by benign PET positive lymph nodes hampers the accurate discrimination of malignant and benign lymph nodes when primary tumour FDG uptake is low (Fig. 5).

The reason why benign lymph nodes elicit FDG uptake is another important issue that needs to be addressed. Glut-1 expression in follicular centre cells has been suggested to explain benign lymph node PET positivity.[14] However, we found no proportional relationship between the degree of follicular hyperplasia and FDG uptake in our previous study.[15] We believe that PET positive benign lymph nodes have higher levels of follicular hyperplasia and express more Glut-1 than true negative benign lymph nodes,[14] but that the low resolution of current PET systems and partial volume effects hamper the elucidation of a proportional relationship between follicular hyperplasia and FDG uptake.[15] Nonetheless, in the present study, we assumed that Glut-1 expression in follicular centre cells may determine benign lymph node FDG uptake, because no other plausible explanation has been suggested to explain FDG uptake in benign lymph nodes. Moreover, in

this regard, we did not notice other lymphadenopathies, such as, histiocytosis and anthracotic pigmentation,[15] tuberculosis,[27] or sarcoid reaction[28–30]; sarcoid reaction in mediastinal lymph nodes has been reported to be a cause of PET positivity in patients with an underlying malignant disease.[28–30] Moreover, tumour-specific immunohistochemical findings in benign lymph nodes with sarcoid reaction may lead to a new paradigm that benign mediastinal lymphadenopathy may be related to certain tumour characteristics.[28] In any cases, proper elucidations of the functional status of glucose transporters appear to be essential if causal relationships between suggested pathogenetic entities and PET positivity are to be derived.

The finding of the present study regarding the correlation between primary tumours and benign lymph nodes with respect to the %Glut-1 expressions (Fig. 4) requires cautious interpretation. In the present study, the proportion of Glut-1 positive follicular centre cells in benign lymph nodes was found to be correlated with the proportion of Glut-1 positive tumour cells in primary tumours, but the r^2 value of 0.1492 obtained indicates that the magnitude of Glut-1 expression in benign lymph nodes is hardly predicted by that in primary tumours. Moreover, Glut-1 staining intensities (another important parameter of Glut-1 functional status) were not found to be correlated between primary tumours and benign lymph nodes. Thus, the absence of a correlation between the FDG uptakes of primary tumours and benign PET positive lymph nodes (Fig. 3) is not incompatible with their weak %Glut-1 expression correlation.

False negative FDG-PET findings for malignant lymph nodes were not the primary concern of this study. In fact, PET negative malignant lymph nodes were excluded, because we specifically set out to investigate the correlation between main NSCLC masses and their PET positive lymph nodes with respect to FDG uptake and Glut-1 expression. In general, FDG uptake by tissues, whether malignant or benign, is influenced by a number of factors,[18] and therefore, it is difficult to pinpoint a singe determinant of FDG uptake. However, in terms of the primary tumours and malignant lymph nodes of NSCLC, it is evident that higher levels of FDG uptake are explained by elevated Glut-1 expression.

The limitation of the present study is about the surgicopathologic localisation of PET positive lesions. The identification of exact locations, especially for lymph nodes, was hard to determine in some cases. We attempted to minimise the limitation by adopting the standard mapping system for lymph node classification.[20]

5. Conclusion

High correlations were found between the primary tumours and metastatic lymph nodes in NSCLC with regard to the FDG uptakes and Glut-1 expressions. This correlation between the FDG uptakes of loco-regional metastatic lymph nodes and primary tumours provides a valuable tool for FDG-PET based mediastinal lymph node discrimination.

Conflict of interest statement

None declared.

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REFERENCES

1. Vansteenkiste JF, Stroobants SG, De Leyn PR, et al. Mediastinal lymph node staging with FDG-PET scan in patients with potentially operable non-small cell lung cancer: a prospective analysis of 50 cases. Leuven Lung Cancer Group. *Chest* 1997;**112**:1480–6.
2. Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003;**348**:2500–7.
3. Higashi K, Ueda Y, Sakurai A, et al. Correlation of Glut-1 glucose transporter expression with [18F]FDG uptake in non-small cell lung cancer. *Eur J Nucl Med* 2000;**27**:1778–85.
4. Chung JK, Lee YJ, Kim SK, Jeong JM, Lee DS, Lee MC. Comparison of [18F]fluorodeoxyglucose uptake with glucose transporter-1 expression and proliferation rate in human glioma and non-small-cell lung cancer. *Nucl Med Commun* 2004;**25**:11–7.
5. Mamede M, Higashi T, Kitaichi M, et al. [18F]FDG uptake and PCNA, Glut-1, and hexokinase-II expressions in cancers and inflammatory lesions of the lung. *Neoplasia* 2005;**7**:369–79.
6. Higashi K, Ueda Y, Ayabe K, et al. FDG PET in the evaluation of the aggressiveness of pulmonary adenocarcinoma: correlation with histopathological features. *Nucl Med Commun* 2000;**21**:707–14.
7. Vansteenkiste JF, Stroobants SG, Dupont PJ, et al. Prognostic importance of the standardized uptake value on (18)F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: an analysis of 125 cases. Leuven Lung Cancer Group. *J Clin Oncol* 1999;**17**:3201–6.
8. Higashi K, Ueda Y, Arisaka Y, et al. 18F-FDG uptake as a biologic prognostic factor for recurrence in patients with surgically resected non-small cell lung cancer. *J Nucl Med* 2002;**43**:39–45.
9. Jeong HJ, Min JJ, Park JM, et al. Determination of the prognostic value of [(18)F]fluorodeoxyglucose uptake by using positron emission tomography in patients with non-small cell lung cancer. *Nucl Med Commun* 2002;**23**:865–70.
10. Sasaki R, Komaki R, Macapinlac H, et al. [18F]fluorodeoxyglucose uptake by positron emission tomography predicts outcome of non-small-cell lung cancer. *J Clin Oncol* 2005;**23**:1136–43.
11. Nguyen XC, Lee WW, Chung JH, et al. FDG uptake, glucose transporter type 1, and Ki-67 expressions in non-small-cell lung cancer: correlations and prognostic values. *Eur J Radiol* 2007;**62**:214–9.
12. Higashi K, Ito K, Hiramatsu Y, et al. 18F-FDG uptake by primary tumor as a predictor of intratumoral lymphatic vessel invasion and lymph node involvement in non-small cell lung cancer: analysis of a multicenter study. *J Nucl Med* 2005;**46**:267–73.

13. Cerfolio RJ, Bryant AS. Ratio of the maximum standardized uptake value on FDG-PET of the mediastinal (N2) lymph nodes to the primary tumor may be a universal predictor of nodal malignancy in patients with nonsmall-cell lung cancer. *Ann Thorac Surg* 2007;**83**:1826–9 [discussion 1829-30].
14. Chung JH, Cho KJ, Lee SS, et al. Overexpression of Glut1 in lymphoid follicles correlates with false-positive (18)F-FDG PET results in lung cancer staging. *J Nucl Med* 2004;**45**:999–1003.
15. Chung JH, Lee WW, Park SY, et al. FDG uptake and glucose transporter type 1 expression in lymph nodes of non-small cell lung cancer. *Eur J Surg Oncol* 2006;**32**:989–95.
16. Lee WW, Chung JH, Jang SJ, et al. Consideration of serum glucose levels during malignant mediastinal lymph node detection in non-small-cell lung cancer by FDG-PET. *J Surg Oncol* 2006;**94**:607–13.
17. Song YS, Lee WW, Chung JH, Park SY, Kim YK, Kim SE. Correlation between FDG uptake and glucose transporter type 1 expression in neuroendocrine tumors of the lung. *Lung Cancer* 2008; in press. doi:10.1016/j.lungcan.2007.11.012.
18. Wahl R. Principles of cancer imaging with fluorodeoxyglucose. In: Wahl R, editor. *Principles and practice of positron emission tomography*. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 100–10.
19. <www.intmed.mcw.edu/clincalc/body.html>.
20. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997;**111**:1718–23.
21. Kurata T, Oguri T, Isobe T, Ishioka S, Yamakido M. Differential expression of facilitative glucose transporter (GLUT) genes in primary lung cancers and their liver metastases. *Jpn J Cancer Res* 1999;**90**:1238–43.
22. Vansteenkiste JF, Stroobants SG, De Leyn PR, et al. Lymph node staging in non-small-cell lung cancer with FDG-PET scan: a prospective study on 690 lymph node stations from 68 patients. *J Clin Oncol* 1998;**16**:2142–9.
23. Gupta NC, Graeber GM, Bishop HA. Comparative efficacy of positron emission tomography with fluorodeoxyglucose in evaluation of small (<1 cm), intermediate (1 to 3 cm), and large (>3 cm) lymph node lesions. *Chest* 2000;**117**: 773–8.
24. Gupta NC, Tamim WJ, Graeber GG, Bishop HA, Hobbs GR. Mediastinal lymph node sampling following positron emission tomography with fluorodeoxyglucose imaging in lung cancer staging. *Chest* 2001;**120**:521–7.
25. Bryant AS, Cerfolio RJ, Klemm KM, Ojha B. Maximum standard uptake value of mediastinal lymph nodes on integrated FDG-PET-CT predicts pathology in patients with non-small cell lung cancer. *Ann Thorac Surg* 2006;**82**:417–22. discussion 422-3.
26. Nakamoto Y, Zasadny KR, Minn H, Wahl RL. Reproducibility of common semi-quantitative parameters for evaluating lung cancer glucose metabolism with positron emission tomography using 2-deoxy-2-[18F]fluoro-D-glucose. *Mol Imaging Biol* 2002;**4**:171–8.
27. Kim YK, Lee KS, Kim BT, et al. Mediastinal nodal staging of nonsmall cell lung cancer using integrated 18F-FDG PET/CT in a tuberculosis-endemic country: diagnostic efficacy in 674 patients. *Cancer* 2007;**109**:1068–77.
28. Karapetis CS, Strickland AH, Yip D, van der Walt JD, Harper PG. PET and PLAP in suspected testicular cancer relapse: beware sarcoidosis. *Ann Oncol*. 2001;**12**:1485–8.
29. de Hemricourt E, De Boeck K, Hilte F, et al. Sarcoidosis and sarcoid-like reaction following Hodgkin's disease. Report of two cases. *Mol Imaging Biol* 2003;**5**:15–9.
30. Maeda J, Ohta M, Hirabayashi H, Matsuda H. False positive accumulation in 18F fluorodeoxyglucose positron emission tomography scan due to sarcoid reaction following induction chemotherapy for lung cancer. *Jpn J Thorac Cardiovasc Surg* 2005;**53**:196–8.