Impact of Lymphoid Follicles and Histiocytes on the False-Positive FDG Uptake of Lymph Nodes in Non-Small Cell Lung Cancer

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Abstract

Purpose Although ^{18}F -fluorodeoxyglucose (FDG) PET/CT has improved the accuracy of evaluating lymph node (LN) staging in non-small cell lung cancer (NSCLC), false-positive results remain a problem. The reason why benign LNs show high FDG uptake is still unclear. The aim of this study was to identify molecular and pathological characteristics of benign LNs showing high FDG uptake.

Materials and Methods We studied 108 mediastinal LNs of pathologically benign nature obtained from 43 patients with NSCLC who underwent FDG PET/CT and surgery. We measured the following parameters in each LN: maximum standardized uptake value (maxSUV), short diameter, maximum Hounsfield unit (maxHU) value, occupied proportions of lymphoid follicles, histiocytes in extrafollicular space and the degree of glucose transporter 1 (Glut1) expression. We compared the parameters between two LN groups according to maxSUV.

Results There were 74 LNs showing $\text{maxSUV} \geq 3.0$ (group 1) and 34 LNs with $\text{maxSUV} < 3.0$ (group 2). The size of LN ($p < 0.001$) and maxHU ($p = 0.003$) in group 1 was

higher than that in group 2. Histologically, the occupied proportions of lymphoid follicles ($p = 0.031$) or histiocytes ($p = 0.004$) were higher in group 1. The Glut1 expression of lymphoid follicles ($p = 0.035$) or histiocytes ($p = 0.005$) was also higher in group 1.

Conclusion Lymphoid follicular hyperplasia and histiocyte infiltration associated with Glut1 overexpression are important molecular and pathological mechanisms for false-positive FDG uptake in benign mediastinal LNs in patients with NSCLC.

Keywords Lymphoid follicle · Histiocyte · Glut1 · FDG · Non-small cell lung cancer · Mediastinal lymph node

Introduction

Lymph node (LN) staging is important for deciding therapeutic plans of non-small cell lung cancer (NSCLC) [1]. ^{18}F -Fluorodeoxyglucose (FDG) PET/CT is known to be superior to CT for evaluating LN metastasis in NSCLC [2–4]. However, false-positive results remain a problem, especially in patients with infection, inflammation or granulomatous diseases [5–8]. Overexpression of glucose transporter 1 (Glut1) is related with both high FDG uptake and malignant potential [9–11]. Glut1 overexpression was noted in physiological conditions with high glucose metabolism and active inflammatory processes [11, 12].

Chung et al. demonstrated that lymphoid follicular hyperplasia was the major pathological factor influencing FDG uptake in false-positive LNs [13]. We frequently found histiocyte infiltration around pigments in the extrafollicular space in addition to lymphoid follicular hyperplasia in mediastinal LNs of patients with NSCLC, so we hypothesized that histiocytes in the extrafollicular space

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might be another important factor causing high FDG uptake. With the aim of identifying molecular and pathological characteristics of benign LNs with high FDG uptake, we compared various findings in CT and pathology according to FDG uptake.

Materials and Methods

Subjects

From September 2004 to May 2007, 43 patients (30 men, 13 women; mean age, 65.2 ± 5.4 years; range, 53–76 years) with NSCLC were enrolled in this study. They underwent FDG PET/CT for staging workup and surgery (primary tumor resection with LN dissection). Patients who had another cancer history, chemotherapy or radiation therapy before surgery were excluded. We reviewed 108 mediastinal LNs of pathologically benign nature obtained from those patients for retrospective analysis. Informed consents were obtained from all patients.

FDG PET/CT

All patients were required to fast for 8 h and encouraged to drink water before the PET/CT (Discovery ST, GE Healthcare, Milwaukee, WI). Non-contrast enhanced CT (Helical, 8 slice, 120 kVp, 80 mAs, 3.79-mm slice thickness) was performed for attenuation correction 50 min after FDG injection. No CT contrast agents were administered. After the CT scan, an emission scan was performed with duration time of 3 min per bed. Acquired data were reconstructed using ordered subset expectation maximization (OSEM) reconstruction (128×128 matrix, 3.27-mm slice thickness, subset: 21, iteration: 2).

The location of LN was defined according to the LN map definition suggested by Mountain and Dresler [14]. The location of each LN was correlated by the consensus of a nuclear medicine physician and thoracic surgeon.

FDG uptake of mediastinal or hilar LNs was measured by PET. LNs were classified into two groups according to maximum standardized uptake value (maxSUV): group 1 (maxSUV ≥ 3.0) and group 2 (maxSUV < 3.0). Then, the short diameter and maximum Hounsfield unit (maxHU) value of each LN were measured with non-contrast-enhanced CT.

Histological Evaluation with Hematoxylin and Eosin (H&E) staining

H&E staining was performed in 108 LNs. Based on the proportions occupied by lymphoid follicles or histiocytes in extrafollicular space in the same histological section, the grade of lymphoid follicles or amount of infiltrated histiocytes was assigned as follows: grade 1, $< 25\%$; grade 2, 25–49%; grade 3, 50–74%; grade 4, 75–100%. Several LNs with different occupied proportions were shown in the histological section (Fig. 1).

Glut1 Immunohistochemical Staining

Formalin-fixed, paraffin sections were immunostained with rabbit anti-Glut1 antibody (1:200). Firstly, each LN section was deparaffinized and incubated with a microwave for 40 min to expose the antigens. Endogenous peroxidase activity was blocked by ethanol mixed with hydrogen peroxide. The section was then washed with saline buffer and incubated with anti-Glut1 antibody (primary antibody) at 37°C for 2 h. After the section incubated with primary antibody was washed with saline buffer, that section was incubated with secondary antibody for 30 min. After washing, 3,3'-diaminobenzidine (DAB) was used as a chromogen by reacting with horseradish peroxidase on the secondary antibody. Finally, the section was counterstained with hematoxylin and mounted. Red blood cells (RBCs) present in each section were used as positive control for Glut1, and the adjacent section incubated with rabbit IgG was used as negative control.

Fig. 1 Occupied proportions of lymphoid follicles and histiocytes in benign lymph nodes were shown. **a** The occupied proportions of both lymphoid follicles and histiocytes were less than 25%. **b** The occupied proportion of lymphoid follicles (arrowhead) was 70%. **c** There were

many histiocytes around anthracotic pigmentation (arrow) as well as several lymphoid follicles (arrowhead). The occupied proportion of histiocytes was 60% and that of lymphoid follicles was 15%. (H&E; $\times 40$)

To measure the degree of Glut1 expression in lymphoid follicles or histiocytes in the extrafollicular space, we developed the semiquantitative method (Glut1 score) that scored the proportion of positive cells as well as staining intensity. Staining intensity was categorized as follows: (1) not stained, (2) equivocal, (3) intense (the same intensity as RBC) and (4) very intense (more intense than RBC). The occupying proportion of positive cells for Glut1 was graded as follows: 1, 1–9%; 2, 10–24%; 3, 25–49%; 4, 50–74%; and 5, 75–100%. Glut1 score was determined by multiplying two values measured in lymphoid follicles or histiocytes in the extrafollicular space, respectively (Figs. 2 and 3).

Statistical Analyses

Independent samples t-test was performed to assess the significance of differences in patient's age, the size and maxHU of LNs between group 1 and group 2. Chi-square test was used to evaluate the significance of differences in the patient's sex and histological type of cancer between the two groups. Mann-Whitney non-parametric two-sample test was performed to assess the significance of difference in the occupied proportions (on H&E staining) and Glut1 scores

Fig. 2 Glut1 immunohistochemical staining in lymphoid follicles (a: staining intensity, b: % of positive cells) was shown. Erythrocytes were used as a positive control. **a** Lymphoid follicle was not stained. **b** There was equivocal staining intensity. **c** The staining intensity of the lymphoid follicle was the same as erythrocytes, which showed intense linear membranous staining. **d** The lymphoid follicle was stained more intensely than the erythrocyte ($\times 200$)

Fig. 3 Glut1 immunohistochemical staining in histiocytes (a: staining intensity, b: % of positive cells) was shown. **a** Histiocytes were not stained. **b-d** There was diffuse, heterogeneous staining in histiocytes. Erythrocytes were used as a positive control ($\times 200$)

of lymphoid follicles between the two groups. The same statistical analysis was applied to assess the significance of difference of infiltrated histiocytes in the extrafollicular space in the two groups.

The Pearson correlation coefficient was used to determine the correlation between maxSUV and these parameters (occupied proportions, Glut1 scores) measured in lymphoid follicles or histiocytes studied from 108 LNs, respectively. The same statistical analysis was used to assess the correlation between maxHU and these parameters.

The coherence between lymphoid follicles and histiocytes (occupied proportions, Glut1 scores) was assessed by using the chi-square test in LNs with maxSUV ≥ 3.0 (group 1). Then, group 1 was divided into three subgroups by the dominance of occupied proportions or Glut1 scores. Dominant follicles (subgroup 1) were defined as the grade of lymphoid follicles that was higher than that of histiocytes in occupied proportions or Glut1 scores. Dominant histiocytes (subgroup 2) were defined as the grade of histiocytes that was higher than that of lymphoid follicles. Similar dominance (subgroup 3) was defined as when the grade of lymphoid follicles and histiocytes was the same. Finally, one-way analysis of variance was performed to determine the significance of difference in maxSUV or maxHU among the three subgroups (dominant follicles, dominant histiocytes and similar dominance). The data were expressed as mean $\pm$ SD. A p value < 0.05 was considered statistically significant (SPSS version 12.0; SPSS Inc.).

Results

There were 74 LNs showing $\text{maxSUV} \geq 3.0$ (group 1) and 34 LNs with $\text{maxSUV} < 3.0$ (group 2). The average of maxSUV was 4.4 ± 1.5 for group 1 and 2.2 ± 0.5 for group 2. There was no significant difference in age, sex and histological type of cancer between the two groups (Table 1).

The size ($p < 0.001$) and maxHU ($p = 0.003$) of LNs in group 1 were higher than those in group 2. On H&E staining, the occupied proportions of lymphoid follicles were significantly higher in group 1 (1.8 ± 0.8) than in group 2 (1.4 ± 0.6) ($p = 0.031$). The occupied proportions of infiltrated histiocytes in the extrafollicular space were also higher in group 1 (2.3 ± 0.8) than in group 2 (1.8 ± 0.9) ($p = 0.004$). When we investigated Glut1 expression by immunohistochemical staining, Glut1 scores of lymphoid follicles or histiocytes were higher in group 1 than in group 2, respectively (lymphoid follicles: 1.9 ± 1.6 vs. 1.2 ± 0.4 , $p = 0.035$; histiocytes: 2.2 ± 1.9 vs. 1.4 ± 1.1 , $p = 0.005$) (Table 2).

However, there was no significant correlation between maxSUV and parameters (occupied proportions, Glut1 scores) measured in lymphoid follicles or histiocytes. When we evaluated the coherence between lymphoid follicles and histiocytes in 74 LNs (group 1), there was no significant correlation in both occupied proportions on H&E staining and Glut1 scores (Tables 3 and 5). We classified 74 LNs (group 1) into three subgroups by the dominance of occupied proportions or Glut1 scores, but there was no significant difference in both maxSUV and maxHU between them (Tables 4 and 6).

A typical case of lymphoid follicular hyperplasia in a benign LN showing high FDG uptake was demonstrated in

Table 1 Comparison of clinical and pathological parameters between the two groups

	Group 1 ^a (n=74)	Group 2 ^a (n=34)	<i>p</i>
Age (years)	64.4±5.1	66.0±4.9	0.122 ^b
Sex			0.228 ^c
Male	48	26	
Female	26	8	
Histology			0.884 ^c
Adenocarcinoma	26	13	
Squamous cell carcinoma	32	15	
Others	16	6	

^a Group 1: benign lymph nodes showing maximum $\text{SUV} \geq 3.0$. Group 2: benign lymph nodes showing maximum $\text{SUV} < 3.0$

^b Independent samples t-test

^c Pearson's chi-square test

Table 2 Computed tomographic (CT) and histological findings of lymph nodes

	Group 1 ^a (n=74)	Group 2 ^a (n=34)	<i>p</i>
Size (mm)	8.8±2.2	6.7±1.6	<0.001 ^b
Maximum Hounsfield units	115.3±75.7	73.2±38.5	0.003 ^b
Occupied proportion			
Lymphoid follicles	1.8±0.8	1.4±0.6	0.031 ^c
Histiocytes	2.3±0.8	1.8±0.9	0.004 ^c
Glut1 score			
Lymphoid follicles	1.9±1.6	1.2±0.4	0.035 ^c
Histiocytes	2.2±1.9	1.4±1.1	0.005 ^c

^a Groups are the same as in Table 1

^b Independent samples t-test

^c Mann-Whitney non-parametric two-sample test

Fig. 4 and a case of histiocyte infiltration around dense pigments in a benign LN showing high FDG uptake in Fig. 5.

Discussion

Association of increased FDG uptake in benign LNs to pathological findings such as inflammatory changes of lymphoid follicles and histiocytes was described by Shim et al., although they did not perform immunohistochemical or quantitative assessment of LNs [15]. On the other hand, Chung et al. investigated pathological factors that affect FDG uptake in benign mediastinal LNs [13]. In their study, the occupied proportion of lymphoid follicles as well as Glut1 expression was significantly higher in the false-positive group than in the true-negative group. Nakagawa et

Table 3 Correlation between occupied proportions of lymphoid follicles and histiocytes on H&E staining in 74 lymph nodes showing maximum $\text{SUV} \geq 3.0$

Occupied proportion	Lymphoid follicles ^a					Total
		Grade 1	Grade 2	Grade 3	Grade 4	
Histiocytes ^a	Grade 1	4	4	4	0	12
	Grade 2	11	12	7	1	31
	Grade 3	11	13	1	0	25
	Grade 4	6	0	0	0	6
Total		32	29	12	1	74

^a Grade of both lymphoid follicles and amount of histiocytes were assigned as follows: grade 1, <25%; grade 2, 25–49%; grade 3, 50–74%; grade 4, 75–100%

Table 4 Comparison of maximum SUV and maximum Hounsfield units among three subgroups by the dominance of occupied proportions in 74 lymph nodes showing maximum SUV $\geq$ 3.0

	Subgroup 1 ^a (n=16)	Subgroup 2 ^a (n=41)	Subgroup 3 ^a (n=17)	<i>p</i>
Maximum SUV	4.2 $\pm$ 1.0	4.5 $\pm$ 1.8	4.5 $\pm$ 1.1	0.724 ^b
Maximum Hounsfield units	113.1 $\pm$ 37.6	126.9 $\pm$ 95.5	89.2 $\pm$ 30.1	0.226 ^b

^a Subgroup 1: dominant follicles, subgroup 2: dominant histiocytes, subgroup 3: similar dominance

^b One-way analysis of variance

al. also reported that FDG uptake in reactive neck LNs was associated with secondary follicles and especially follicular dendritic cells of secondary follicles [16].

Because activated histiocytes can show increased FDG uptake and Glut1 overexpression, it was natural to assume that histiocyte infiltration into benign LNs can also cause false-positive FDG uptake [12, 17]. However, the impact of infiltrated histiocytes in the extrafollicular space on Glut1 expression as well as FDG uptake was not studied well.

Our primary concern in this study was whether infiltrated histiocytes could equally affect FDG uptake to lymphoid follicles in benign LNs of patients with NSCLC. From this study, occupied proportions and Glut1 scores in lymphoid follicles or histiocytes were higher in group 1 (LNs with maxSUV $\geq$ 3.0). However, there was no significant correlation between lymphoid follicles and histiocytes (Tables 3 and 5) and no significant difference in maxSUV among the three subgroups (dominant follicles, dominant histiocytes and similar dominance) for both occupied proportions and Glut1 scores in group 1 (Tables 4 and 6). Therefore, infiltrated histiocytes are another important factor that can affect false-positive FDG uptakes.

However, FDG uptake did not increase in proportion to the grade of these parameters (occupied proportions, Glut1 scores) in our study. In previous articles, Glut1 expression in lymphoid follicular hyperplasia showed no correlation with FDG uptake in benign LNs, and there was no relationship between maxSUV and the number of total lymphoid follicles [16, 18]. However, Tawakol et al. demonstrated that vascular macrophage activity can be quantified with FDG PET by showing a strong correlation between FDG uptake and macrophage density [19]. Considering previous articles, therefore, we can induce other factors to affect FDG uptake.

First of all, most LNs included the mixture of occupied proportions of lymphoid follicles and histiocytes to a various degree (Tables 3 and 5), and it might be very difficult to assess correlation with FDG uptake by using a single parameter. However, there was also no correlation when we assessed the relationship between FDG uptake and several parameters by adding or multiplying them. Those results suggested that other factors than the mixture of them, for example, cellularity [20, 21], several enzymes or cytokines, to activate macrophages and variable cellular characteristics could affect FDG uptake in benign LNs.

Mark et al. reported that the cellularity increased around the calcification after the inflammation of vessels and resulted in increased FDG uptake [20]. So, we can also predict that the similar mechanism may be involved in mediastinal LNs. Malide et al. reported that macrophages transformed from monocytes were activated by extrinsic factors, and it caused increased FDG uptake by movement of Glut1 from the cytoplasm to cell membrane [12].

Other possible reasons why FDG uptake did not increase in proportion to their grade can be attributed to several limitations of the methodology. First, it was not sufficient to characterize lymphoid follicles and histiocytes in extrafollicular space because they were analyzed with the occupied proportions (on H&E staining) or Glut1 expres-

Fig. 4 A 64-year-old male with squamous cell carcinoma underwent FDG PET/CT. **a** Unenhanced CT showed high attenuated lymph node (arrow) in the left hilum. **b** FDG PET showed increased uptake in the

left hilar lymph node (arrow). **c** Histology showed many lymphoid follicles (arrow) (H&E stain, $\times$ 40). **d** There was intense linear membranous Glut1 staining in each lymphoid follicle ($\times$ 200)

Fig. 5 A 70-year-old female with adenocarcinoma underwent FDG PET/CT. **a** Unenhanced CT showed a highly attenuated subcarinal lymph node (arrow). **b** FDG PET showed increased uptake in the

subcarinal lymph node (arrow). **c** Histology showed many histiocytes with anthracotic pigmentation (arrow) (H&E stain, $\times 40$). **d** There was intense heterogeneous Glut1 staining in histiocytes ($\times 200$)

sions (on Glut1 staining) only. It would be helpful to understand the correlation among those parameters if further characterization of them, for example, immunohistochemical staining of histiocytes such as CD68 was performed. Second, we did not consider the partial volume effect in PET/CT, although the size of LN could be a confounding factor of maxSUV. However, it was very difficult to apply size to maxSUV because its overall range was very narrow (range, 5.1–11.0 mm) including group 1 and 2. It was also associated with deciding the cutoff value of maxSUV. Several candidates for the cutoff value could be considered, but we decided the cutoff value of maxSUV (3.0) according to the clinically diagnostic criterion in our hospital because of these limitations. Third, it was difficult to match LNs dissected by surgery to the PET/CT image exactly. Especially, many LNs could be dissected from a single location, and it was possible to match a wrong LN to the PET/CT image. So, we included a single LN dissected from a single location into the study group and selected LNs proximal to the hilum to reduce selection bias because LNs distal to the hilum could include various locations by LN map definition. With this manipulation, the average number of selected LNs was 2.5 in each patient. Fourth,

many LNs showed high attenuation on CT. High attenuation (or high CT numbers) could result in high PET attenuation coefficients, leading to an overestimation of FDG uptake [22].

Therefore, these factors, including limitations, were thought to induce the variable distribution of FDG uptake in benign LNs.

In addition to glucose uptake, the granulomatous or reactive inflammatory process in LNs can also cause calcification or high attenuation (compared with adjacent great vessels) on CT [23]. Pathologically, mediastinal LNs with false-positive FDG uptake and high attenuation show lymphoid follicular hyperplasia and histiocytes with anthracotic pigmentation [15]. In our study, there was a higher degree of maxHU in those LNs showing increased FDG uptake (group 1) (Table 2). However, there was no significant correlation between maxHU and parameters (occupied proportions, Glut1 scores) measured in lymphoid follicles or histiocytes. We investigated which one was the major factor to affect CT attenuation of LN between lymphoid follicles and histiocytes around pigment from 74 LNs showing maxSUV ≥ 3.0 (group 1) (Table 3). When we assessed the significance of differ-

Table 5 Correlation between Glut1 scores of lymphoid follicles and histiocytes in 74 lymph nodes showing maximum SUV ≥ 3.0

		Glut1 score of lymphoid follicles					Total
		1	2	3	4	≥ 5	
Glut1 score of histiocytes	1	30	3	0	8	1	42
	2	8	2	0	2	2	14
	3	2	0	0	1	0	3
	4	3	1	1	1	0	6
	≥ 5	6	2	0	1	0	9
Total		49	8	1	13	3	74

Table 6 Comparison of maximum SUV and maximum Hounsfield units among the three subgroups by the dominance of Glut1 score in 74 lymph nodes showing maximum SUV ≥ 3.0

	Subgroup 1 ^a (n=17)	Subgroup 2 ^a (n=24)	Subgroup 3 ^a (n=33)	<i>p</i>
Maximum SUV	4.6 $\pm$ 1.7	4.4 $\pm$ 0.9	4.4 $\pm$ 1.7	0.906 ^b
Maximum Hounsfield units	99.1 $\pm$ 28.9	112.2 $\pm$ 66.1	125.9 $\pm$ 96.1	0.486 ^b

^a Subgroup 1: dominant follicles, subgroup 2: dominant histiocytes, subgroup 3: similar dominance

^b One-way analysis of variance

ence in maxHU among three subgroups (dominant follicles, dominant histiocytes and similar dominance), there was no significant difference in maxHU among them (Table 4). From these results, CT attenuation represented with maxHU did not increase in proportion to the occupied proportions of lymphoid follicles or histiocytes, and did not show dominance between lymphoid follicles and histiocytes. This suggested that CT attenuation was associated with other factors in addition to previously mentioned factors. Especially, we sometimes observed microcalcification in LNs, and this could affect maxHU, regardless of lymphoid follicles or histiocytes. Therefore, it could be possible to have different results when measuring maxHU excluding microcalcification, although it is very difficult to measure maxHU when excluding it.

In conclusion, both occupied proportions and Glut1 scores of lymphoid follicles or histiocytes in the extrafollicular space were higher in group 1 (LNs with maxSUV $\geq$ 3.0) than in group 2 (LNs with maxSUV<3.0), when pathological findings were correlated with FDG PET/CT findings in benign mediastinal LNs of patients with NSCLC. Moreover, the distribution of the occupied proportions and Glut1 scores showed variable features without dominance of FDG uptake between lymphoid follicles and infiltrated histiocytes in group 1. Therefore, infiltrated histiocytes as well as lymphoid follicles are thought to be important mechanisms for increased FDG uptake in benign mediastinal LNs.

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Conflict of Interest We declare that we have no conflict of interest.

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