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ORIGINAL ARTICLE

Characteristics of Metastatic Mediastinal Lymph Nodes of Non-Small Cell Lung Cancer on Preoperative F-18 FDG PET/CT

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Abstract
Purpose The aim of this study was to evaluate the characteristics of PET and CT features of mediastinal metastatic lymph nodes on F-18 FDG PET/CT and to determine the diagnostic criteria in nodal staging of non-small cell lung cancer.
Methods One hundred four non-small cell lung cancer patients who had preoperative F-18 FDG PET/CT were included. For quantitative analysis, the maximum SUV of the primary tumor, maximum SUV of the lymph nodes (SUVmax), size of the lymph nodes, and average Hounsfield units (aHUs) and maximum Hounsfield units (mHUs) of the lymph nodes were measured. The SUVmax, SUV ratio of the lymph node to blood pool (LN SUV/blood pool SUV), SUV ratio of the lymph node to primary tumor (LN SUV/primary tumor SUV), size, aHU, and mHU were compared between the benign and malignant lymph nodes.
Results Among 372 dissected lymph node stations that were pathologically diagnosed after surgery, 49 node stations were malignant and 323 node stations benign. SUVmax, LN SUV/blood pool SUV, and size were significantly different between the malignant and benign lymph node stations ($P<0.0001$). However, there was no significant difference in LN SUV/primary tumor SUV ($P=0.18$), mHU ($P=0.42$), and aHU ($P=0.98$). Using receiver-operating characteristic curve analyses, there was no significant difference among these three variables (SUVmax, LN SUV/blood pool SUV, and size). The optimal cutoff values were 2.9 for SUVmax, 1.4 for LN SUV/blood pool SUV, and 5 mm for size. When the cutoff value of SUVmax≥2.9 and size≥5 mm were used in combination, the positive predictive value was 44.2 %, and the negative predictive value was 90.9 %. When we evaluated the results based on the histology of the primary tumor, the negative predictive value was 92.3 % in adenocarcinoma (cutoff values of SUVmax≥2.3 and size≥5 mm) and 97.2 % in squamous cell carcinoma (cutoff values of SUVmax≥3.6 and size≥8 mm), separately.
Conclusions In the lymph node staging of non-small cell lung cancer, SUVmax, LN SUV/blood pool SUV, and size show statistically significant differences between malignant and benign lymph nodes. These variables can be used to differentiate malignant from benign lymph nodes. The combination of the SUVmax and size of lymph node might have a good negative predictive value.

Keywords F-18 FDG · PET/CT · Non-small cell lung cancer · Mediastinal lymph nodes

Introduction

Lung cancer is one of the leading causes of cancer-related death [1]. According to cancer statistics in Korea, the crude death rate of lung cancer is 31.3 % and ranked first as a cause of death among total cancers [2]. To reduce mortality and improve the survival rate of lung cancer patients, accurate diagnosis and appropriate treatment are important. Lymph node staging is one of the important elements that can affect treatment guidelines. For diagnosis and clinical staging of lung cancer, chest computed tomography (CT) has been used routinely. However, there is no definite criterion to determine lymph node metastasis, except the size of the lymph nodes or infiltrative features. Therefore, chest CT has shown low reliability in many studies of lymph node staging in lung cancer [3, 4]. Mediastinal lymph node biopsy using mediastinoscopy

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has high accuracy. However, this is an invasive method because it requires a surgical incision to the neck and general anesthesia.

F-18 fluoro-2-deoxyglucose positron emission tomography (FDG PET) detects cancer by increased glucose metabolism in cancer tissue compared to normal tissue. F-18 FDG PET has been used as a tool that can complement chest CT [5, 6]. The metabolic changes in tissue appear in advance of the anatomical changes. Therefore, F-18 FDG PET not only complements anatomical imaging such as chest CT, but also has highly diagnostic results [7–9]. However, F-18 FDG can be taken up by various physiological changes or benign pathological lesions such as inflammation [10, 11].

Analysis of the characteristics of malignant lymph nodes in F-18 FDG PET/CT for distinguishing between benign change and malignant metastasis will be a great help in determining the treatment of patients with lung cancer and improving the survival rate.

F-18 FDG PET/CT is a hybrid imaging technique composed of PET and CT. The aim of this study was to evaluate the characteristics of the PET and CT features of F-18 FDG PET/CT in mediastinal metastatic lymph nodes and to determine the diagnostic criteria for nodal staging of non-small cell lung cancer.

Materials and Methods

One hundred four non-small cell lung cancer patients (63 male, 41 female) who underwent preoperative F-18 FDG PET/CT for staging from January 2007 to June 2012 at our institute were included retrospectively. Mean age was 64.5± 0.7 years (range 31–80 years). The most frequent lung cancer type was adenocarcinoma. Others were squamous cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, and large cell carcinoma. One patient had two kinds of cancer simultaneously (Table 1). Three hundred seventy-two lymph node stations were identified pathologically after surgical resection.

Table 1 Characteristics of patients

Characteristics	Number of patients (%)
Male/female	63/41
Mean age (years)	64.5±0.7[†]
Histological type	
Adenocarcinoma	65 (62.5 %)
Squamous cell carcinoma	31 (29.8 %)
Adenosquamous carcinoma	5 (4.7 %)
Sarcomatoid carcinoma	1 (1 %)
Large cell carcinoma	1 (1 %)
Synchronous cancer (adenocarcinoma + squamous cell carcinoma)	1 (1 %)

[†] Mean ± standard deviation

PET/CT Procedure

All patients fasted at least 6 h before F-18 FDG administration. F-18 FDG PET/CT imaging was performed 60 min after injection of approximately 370 MBq of F-18 FDG using a dedicated PET/CT scanner (Discovery STE®, GE Healthcare, Milwaukee, WI, USA). At 60 min after administration of F-18 FDG, low-dose CT from the base of the skull to the proximal thighs was carried out for the purpose of attenuation correction and localization by a continuous spiral technique using an eight-slice CT (140 KeV, 40–120 mA adjusted to the patients' body weights).

PET images were acquired for 2½ min per bed position in two-dimensional mode. The obtained images were reconstructed using an iterative reconstruction algorithm.

Data Analysis

For semiquantitative analysis, a region of interest was placed over the primary lung cancer lesion, and the maximum standardized uptake value (SUVmax) was measured. SUVmax, size (short diameter), maximum Hounsfield units (mHUs), and average Hounsfield units (aHUs) of surgically resected mediastinal lymph node stations were measured. On the assumption that the largest one has the highest possibility of malignancy, we measured the SUVmax, size, and HUs of the largest lymph node of that nodal station.

To compare with background radioactivity, the average standardized uptake value (SUVave) of the aortic arch was measured.

Then, the ratio of the lymph node SUVmax to the primary cancer lesion SUVmax (LN SUV/primary tumor SUV) and ratio of the lymph node SUVmax to the aortic arch SUVave (LN SUV/blood pool SUV) were calculated.

Statistical Analysis

Statistical analyses were performed using MedCalc software (version 12.3.0; MedCalc, Mariakerke, Belgium). Differences were considered statistically significant when P values were less than 0.05. The significant difference between malignant and benign lymph nodes was tested by Student's t-test for size, SUVmax, mHU, aHU, LN SUV/primary tumor SUV, and LN SUV/blood pool SUV. Receiver-operating characteristic (ROC) curve analysis was used to compare the diagnostic power of each variable. The optimal cutoff value of these variables producing maximum sensitivity plus specificity for

detecting metastatic lymph nodes was determined from ROC analysis.

Results

Primary Tumor and Lymph Node Stations

Of the 104 lung cancer patients, 372 lymph node stations were confirmed pathologically. Three hundred twenty-three lymph node stations were benign, and 49 lymph node stations were malignant.

In preoperative PET/CT, the average of SUVmax of the primary lung lesions was 9.1 (95 % CI: 8.1 to 10.2, range: 1.4 to 30.4). The average of SUVave of the blood pool in the aorta or aortic arch was 1.6 (95 % CI: 1.5 to 1.7, range: 0.8 to 2.6).

Mean SUVmax of the malignant lymph node stations (3.7± 2.9) was higher than that of benign ones (2.1±0.9, $P<0.0001$). The size was larger and LN SUV/blood pool SUV was higher in malignant lymph nodes than in benign ones ($P<0.0001$). There was no significant difference in LN SUV/primary tumor SUV, mHU, and aHU (Table 2).

In 49 malignant lymph node stations, 32 were adenocarcinoma, and 14 were squamous cell carcinoma. Mean SUVmax of lymph nodes of adenocarcinoma was 3.1±2.5 and that of squamous cell carcinoma was 5.1± 3.4 ($P=0.01$). The sizes were a little larger in squamous cell carcinoma than in adenocarcinoma ($P=0.05$). There were no significant differences in the LN SUV/blood pool SUV, LN SUV/primary tumor SUV, mHU, and aHU (Table 3).

Diagnostic Value in SUVmax, Size, and LN SUV/Blood Pool SUV

By ROC curve analysis, the diagnostic values were compared among SUVmax, size, and LN SUV/blood pool SUV, which showed a significantly different value between malignant lymph nodes and benign lymph nodes. Area under the curve (AUC) of the SUV max was 0.701, AUC of size was 0.721, and AUC of the LN SUV/blood pool SUV was 0.700. There was no significant difference in AUC among the three variables.

The cutoff value of SUVmax producing maximum sensitivity plus specificity was 2.9 (sensitivity 46.9 %, specificity 90.4 %). The cutoff value for size was 5 mm (sensitivity 89.8 %, specificity 41.5 %). The cutoff value of LN SUV/blood pool SUV was 1.4 (sensitivity 69.4 %, specificity 64.7 %, Table 4). When the cutoff values of SUVmax≥2.9 and size≥5 mm were used in combination, the positive predictive value was 44.2 %, and the negative predictive value was 90.9 %.

The cutoff values of SUVmax, size, and LN SUV/blood pool SUV based on the histology of the primary tumor is shown in Table 5. The cutoff value of SUVmax was 2.3 (sensitivity 56.3 %, specificity 72.2 %), size was 5 mm (sensitivity 59.4 %, specificity 64.2 %), and LN SUV/blood pool SUV was 1.4 (sensitivity 71.9 %, specificity 60.6 %) in adenocarcinoma. When the cutoff values of SUVmax≥2.3

Table 2 Characteristics of mediastinal lymph node stations in PET/CT

	Benign LN	Malignant LN	*P* value
Number	323	49	
SUVmax	2.1±0.9	3.7±2.9	<0.0001
Size (short diameter, mm)	4.3±2.1	6.4±2.9	<0.0001
LN SUV/blood pool SUV	1.4±0.7	2.4±2.0	<0.0001
LN SUV/primary tumor SUV	0.4±0.3	0.4±0.3	0.18
mHU	137±235	81 ±40	0.10
aHU	44±88	33±32	0.38

All data represent mean ± standard deviation

LN: lymph node

SUV: standard uptake value

mHU: maximum Hounsfield units

aHU: average Hounsfield units

Table 3 Characteristics of malignant lymph node stations in PET/CT

Pathology	Adenocarcinoma	Squamous cell carcinoma	*P* value
Number	32	14	
SUVmax	3.1±2.5	5.1±3.4	0.01
Size (short diameter, mm)	5.8±2.5	7.8±3.6	0.05
LN SUV/blood pool SUV	2.1±2.0	2.9±2.0	0.07
LN SUV/primary tumor SUV	0.4±0.3	0.5±0.4	0.38
mHU	82±40	78±42	0.88
aHU	40±32	24±29	0.16

All data represent mean ± standard deviation

LN: lymph node

SUV: standard uptake value

mHU: maximum Hounsfield units

aHU: average Hounsfield units

Table 4 ROC-derived criteria and accuracy

	Sensitivity(%)	Specificity(%)	AUC
SUVmax≥2.9	46.9	90.4	0.701
Size (short diameter, mm)≥5	89.8	41.5	0.721
LN SUV/blood pool SUV≥1.4	69.4	64.7	0.700

ROC: receiver operating characteristic

AUC: area under the curve

SUV: standardized uptake value

LN: lymph node

Table 5 ROC-derived criteria based on the histology of the primary tumor

Histology	Criteria	Sensitivity(%)	Specificity(%)	AUC
Adenocarcinoma	SUVmax≥2.3	56.3	72.2	0.644
	Size (short diameter, mm)≥5	59.4	64.2	0.702
	LN SUV/blood pool SUV≥1.4	71.9	60.6	0.667
Squamous cell carcinoma	SUVmax≥3.6	92.0	64.3	0.803
	Size (short diameter, mm)≥8	50.0	88.0	0.787
	LN SUV/blood pool SUV≥1.8	64.3	81.9	0.766

and size≥5 mm were used in combination, the negative predictive value was 92.3 %. The cutoff value of SUVmax was 3.6 (sensitivity 92.0 %, specificity 64.3 %), size was 8 mm (sensitivity 50.0 %, specificity 88.0 %), and LN SUV/blood pool SUV was 1.8 (sensitivity 64.3 %, specificity 81.9 %) in squamous cell carcinoma. When the cutoff values of SUVmax≥3.6 and size≥8 mm were used in combination, the negative predictive value was 97.2 %.

Discussion

The present study revealed that SUVmax, LN SUV/blood pool SUV, and size are significantly different between malignant and benign lymph node stations. These variables can be used to differentiate malignant lymph nodes from benign ones. The combination of the SUVmax and size of the lymph nodes might result in good negative predictive value.

Chest CT is a conventional anatomic imaging method and widely used to evaluate mediastinal lymph node metastasis in the lung cancer patient. Being larger than 10 mm is one of the most commonly used criteria for metastatic lymph nodes [12, 13]. However, this criterion shows variable diagnostic results of 41-67 % for sensitivity and 79-86 % for specificity [4, 14, 15]. Another anatomic imaging method, MRI, showed no significant difference for the diagnosis of metastatic lymphadenopathy in lung cancer either. Webb et al. [15] reported that in a prospective study including 170 lung cancer patients, MRI and CT showed no different results for the diagnosis of mediastinal lymph node metastasis. The result of Bonomo et al.'s study was also similar [3].

F-18 FDG PET could improve the diagnostic value more than the conventional anatomic images in the staging of lung cancer patients. In a previous meta-analysis, PET was significantly more correct than CT for the diagnosis of nodal metastases. Mean sensitivity and specificity were 79 and 91 % for PET and 60 % and 77 % for CT [16]. In another meta-analysis, the diagnostic ability for N-staging was similar; the sensitivity and specificity of F-18 FDG PET are 88 and 92 %, which is superior to CT with 65 and 76 % [17]. The hybrid PET/CT was more accurate than PET alone or CT alone for lymph node diagnosis in lung cancer staging [18]. However, the diagnostic criteria for PET and CT were not definitely defined in these studies.

Even though F-18 FDG PET has excellent results for lung cancer staging, false-positive or false-negative results could occur frequently. False-positive uptake could be caused by granulation tissue, inflammatory change, physiological uptake, or artifacts [19–22], whereas false-negative results could be due to small lesion size, micrometastasis, or the short distance of LN from the FDG-avid pleural lesion and huge primary mass [17, 23, 24]. Therefore, precise diagnostic criteria for mediastinal lymph node staging in lung cancer using F-18 FDG PET/CT are needed.

In this study, the lymph node SUVmax, ratio of lymph node SUVmax and aortic arch SUVave (LN SUV/blood pool SUV), and size were found to be meaningful variables for differentiating metastatic lymph nodes.

SUVmax is widely used as an indicator for the diagnosis of lymph node metastasis in lung cancer patients [25, 26]. Kumar et al. [26] reported that malignant mediastinal lymph nodes showed higher SUVmax, and the cutoff value was 2.5. In our study, the cutoff value for SUVmax was 2.9 using ROC curve analysis. However, it showed low sensitivity of 46.9 %. The reason for the low sensitivity is thought to be the many micrometastases of lymph nodes that were beyond the limitations of the resolution of PET but were surgically confirmed. An et al. [11] reported a cutoff value of 4.4, which was slightly higher than our result. The reason is thought to be that they included a lot of patients with inflammatory lung disease.

The LN SUV/blood pool SUVs were significantly higher in malignant lymph nodes. Blood pool SUVave was used as a normal reference [27]. Tournoy et al. [25] selected liver SUVave as background activity and reported that the ratio of lymph node SUVmax to liver SUVave (SUVmax/SUVliver) was higher in malignant mediastinal lymph nodes in lung cancer patients. We selected blood pool SUV as background activity, and LN SUV/blood pool SUV was higher in malignant lymph nodes.

There are reports that F-18 FDG uptake by mediastinal lymph nodes was correlated with that by the primary non-small cell lung cancer [28, 29]. Under the assumption that the

ratio of two SUV values would be the significant variable, we evaluated the LN SUV/primary tumor SUV ratio. However, LN SUV/primary tumor SUV was not significantly different between malignant and benign lymph nodes in our study.

There are reports on increasing the diagnostic accuracy of F-18 FDG PET/CT in mediastinal lymph node staging of lung cancer, such as dual-time-point imaging [30]. The SUV of delayed imaging was the most accurate variable for lymph node staging. However, it is time-consuming in busy daily PET practice.

Size, mHU, and aHU of unenhanced CT were also evaluated in this study for diagnostic criteria. Of three variables, only size was significantly different between malignant and benign lymph nodes. The cutoff value for size was 5 mm. The cutoff value for size is relatively small because we included all the surgically resected lymph node stations even though they were very small on unenhanced CT. The mean size of benign lymph nodes was 4.3±2.1 mm, and the mean value of malignant lymph nodes was 6.4±2.9 mm, but there were many small benign lymph nodes that were hard to measure on unenhanced CT.

A previous study reported the cutoff value of mHU in staging PET/CT was 74 [11]. In our study, aHU and mHU were not significantly different between malignant and benign lymph nodes, but mHU tended to be higher in benign lymph nodes ($P=0.10$). It is also suggested that we evaluated all the surgically resected lymph node stations that may have had previous granulomatous inflammatory lesions in metastatic lymph nodes. More studies are needed to evaluate the relationship between mHU and the pathological state.

Our study showed a relatively low diagnostic value of F-18 FDG PET/CT for malignant mediastinal lymph nodes in lung cancer patients. Adenocarcinoma is known for low FDG-avidity [29]. In this study, many adenocarcinoma cases were included, and adenocarcinoma showed a significantly lower SUVmax than squamous cell carcinoma. Therefore, it could be one of the reasons for low sensitivity in our study. In one prospective study for diagnostic accuracy of integrated F-18 FDG PET/CT, the accuracy was also low for replacing invasive intrathoracic lymph node staging in lung cancer patients [25]. So far, mediastinoscopy has remained the gold standard for reliable mediastinal staging. Mediastinoscopy shows good diagnostic results with sensitivity 81 %, specificity 100 %, negative predictive value 91 %, and positive predictive value 100 % [31]. However, mediastinoscopy is an invasive method performed under general anesthesia. Therefore, the European Society of Thoracic Surgeons (ESTS) suggests guidelines for preoperative lymph node staging for non-small cell lung cancer including PET findings [32]. They suggested mediastinoscopy should remain the gold standard for superior mediastinal lymph node staging for primary staging. This invasive procedure can be omitted in patients with peripheral tumors and negative mediastinal PET findings. However, PET-positive findings in the mediastinum should always be histologically confirmed. For this purpose, the diagnostic criteria for mediastinal metastatic lymph nodes on F-18 FDG PET/CT should be characterized, and our study can give some clues. In this study, the cutoff values of SUVmax≥2.9 and size≥5 mm used in combination give a negative predictive value of 90.9 %. When we evaluate the results based on the histology of the primary tumor, the negative predictive value was 92.3 % in adenocarcinoma (cutoff values of SUVmax≥2.3 and size≥5 mm) and 97.2 % in squamous cell carcinoma (cutoff values of SUVmax≥3.6 and size≥8 mm).

This study has some limitations. It was a retrospective study and included only patients with operable lung cancer patients, which may have caused a selection bias. Only ipsilateral mediastinal lymph nodes were included, and the number of lymph node metastases was low. Although we compared the metastatic lymph node stations based on their histology, each number was also small. Further studies including larger numbers of pathologically proven metastatic lymph nodes are needed. Another limitation of this study is that inaccuracies may occur when measuring the size of very small lymph nodes.

Conclusion

In preoperative F-18 FDG PET/CT of lung cancer patients, the SUVmax, LN SUV/blood pool SUV, and size of lymph nodes were significantly high in metastatic mediastinal lymph nodes. The cutoff values were 2.9 for SUVmax, 5 mm for size, and 1.4 for LN SUV/blood pool SUV. In adenocarcinoma, these were 2.3 for SUVmax and 5 mm for size, and in squamous cell carcinoma, these were 3.6 for SUVmax and 8 mm for size. The combination of SUVmax and size of the lymph node might result in good negative predictive values.

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Conflict of interest None

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