의학석사 학위논문

Additive Roles of F-18 FDG PET/CT for the Prediction of Silent Brain Metastasis in Patients with T1 and T2 Adenocarcinoma of Lung

조기 폐선암에서 뇌전이에 대한 F-18 FDG 양전자단층촬영술의 추가적 예측능

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A thesis of the Degree of Master of Science in Medicine

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The Department of Nuclear Medicine

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by

Bolormaa Ganbaatar

A thesis submitted to the College of Medicine in Partial fulfillment of the requirements for the Degree of Master of Science in Medicine (Nuclear Medicine) at Seoul National University College of Medicine

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Abstract

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Objective: F-18 fluorodeoxyglucose (FDG) PET/CT is widely used for the diagnosis and staging in patients with non-small cell lung cancer (NSCLC). However, its relatively low sensitivity to detect brain metastasis is one of limitations of F-18 FDG PET/CT, as brain metastases are not uncommon even in patients with early stage NSCLC. The purpose of this study was to evaluate an additive role of F-18 FDG PET/CT to predict brain metastasis in patients with T_1 and T_2 adenocarcinoma of lung.

Methods: A total of 395 neurologically asymptomatic lung adenocarcinoma patients with T_1 and T_2 on chest CT from 2011 to 2014 were enrolled, consecutively. All patients underwent chest CT, F-18 FDG PET/CT and brain magnetic resonance imaging (MRI) as a part of initial staging. TNM-staging (T_{CT}, N_{CT} and M_{CT}) were determined on diagnostic CT scans according to the AJCC staging system (7^{th} edition). Standardized uptake value (SUV) and metabolic-volumetric parameters of primary tumors (T_{PET}) were obtained and N/M re-staging (N_{CT+PET}, M_{CT+PET})

were determined on F-18 FDG PET/CT. Brain metastasis was determined on initial brain MRI and/or follow-up imaging studies up to 6 months. EGFR mutation and other clinical status were determined by medical record reviews. Receiver operating curve (ROC) analyses were performed to evaluate the optimal cutoff value for the continuous parameters. Logistic regression analyses were done to evaluate both clinical and PET metabolic parameters to predict brain metastases in lung adenocarcinoma. T, N and M factors by CT and FDG PET were compared with each other by NcNemar test.

Result: Of 395 patients enrolled, 51 patients (13%) had brain metastasis on brain MRI (n=43) and/or follow-up imaging studies (n=8). Optimal cut-offs and area under the curves (AUCs) to predict brain metastasis for metabolic parameters of primary tumors (T_{PET}) on F-18 FDG PET: SUVpeak, TLG, and SUVmean were 7.5; 0.684, 40.5; 0.718, 4.5; 0.646, respectively. The rates of silent brain metastasis were 6.9%, 5.2%, 8.3% in SUVpeak, TLG, SUVmean of the cut-offs or less, whereas the rates were 20.5%, 20.4% and, 21.2% in above the cut-offs, respectively ($P<0.001$). The sensitivity and specificity of F-18 FDG PET for detecting mediastinal lymph node metastases were 52.1% and 81.1%, whereas those of chest CT were 23.3% and 92.1%, respectively ($P<0.01$ by McNemar test). F-18 FDG PET/CT detected distant metastases in 123 with extrathoracic metastasis except brain in 26 patients in addition to the thoracic metastasis (n=97) on chest CT. In univariate analysis, metabolic parameters of primary tumors (T_{PET}) on FDG PET, that is, SUVpeak, TLG, and 2.5SUVmean had hazard ratios (HRs) of 3.69 ($P<0.001$), 4.71 ($P<0.001$), and 2.95 ($P<0.001$), respectively, while T-staging by CT (T_{CT}) having hazard ratio

(HR) of 1.98 (P=0.027). HRs for N-staging by CT (N_{CT}) and FDG PET (N_{CT+PET}) were 12.6 (P<0.001) and 13.5 (P<0.001), and HRs of intrathoracic M-staging by CT (M_{CT}) and additional extrathoracic M-staging by FDG PET (M_{CT+PET}) were 11.1 (P<0.001) and 57.4 (P<0.001), respectively. In multivariate analysis, N_{CT} and M_{CT} staging on CT (HR 5.41; P<0.001, HR1.98; P<0.001) and N_{CT+PET} and M_{CT+PET} staging (HR 3.1; P=0.056, HR37.3; P<0.001) had significant associations with the occurrence of brain metastasis, respectively. The rate of silent brain metastasis was 0.6% in M_0 and N_0 and 0.5% in Stage IIA or less by F-18 FDG PET/CT, and those were 0.9% and 1.3% by CT in patients with T1 and T2 lung adenocarcinoma on chest CT.

Conclusion: Silent brain metastasis was not uncommon and its incidence rate was more than 1%, even in the early stage of lung adenocarcinoma in our data. Additive roles of F-18 FDG-PET/CT to predict silent brain metastasis in patients with T_1 and T_2 lung adenocarcinoma on chest CT were definitely achieved by detecting extrathoracic metastasis (M_{CT+PET}). N-staging (N_{CT+PET}) and higher metabolic activity (T_{PET}) on F-18 FDG PET also had significant associations with silent brain metastasis, but their additive roles to predict brain metastasis had marginal statistical significances, in this retrospective study. NCCN guideline (ver 2.2018) optionally recommends brain MRI with contrast in stage IB of non-small cell lung cancer (NSCLS). Further study with a large population of stage I NSCLC and a prospective design will be needed to define the additive roles to guide optional use of brain MRI study in early stage of NSCLC.

Keywords: non-small cell lung carcinoma (NSCLC), adenocarcinoma, brain metastasis, F-18 FDG-PET/CT, metabolic parameter

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List of abbreviations and symbols

FGD: Flurodeoxyglucose

PET/CT :Positron Emission Tomography / Computed Tomography

MRI : Magnetic Resonant Image

NSCLC : Non Small Cell Lung Carcinoma

TNM : Tumor, Nodal , Metastases

T_{CT} : T-staging based on Computed Tomography

N_{CT} : N-staging based on Computed Tomography

M_{CT} : M-staging based on Computed Tomography

N_{CT+PET} : N-staging based on Computed Tomography / Positron Emission Tomography

M_{CT+PET} : M-staging based on Computed Tomography / Positron Emission Tomography

T_{PET} : PET parameters measured from primary tumor

SUVpeak : average of Standardized Uptake Value

SUVmean : mean Standardized Uptake Value

MTV : Metabolic Tumour Volume

TLG : Total Lesion Glycolysis

RECIST : Response Evolution Criteria In Solid Tumor

ROC : Receiver-Operating Characteristic

AUC : Area Under the Curve

ECOG : Eastern Cooperative Oncology Group

EGFR : Epidermal Growth Factor Recepter

I. INTRODUCTION

Lung cancer is one of the most common malignant tumors and has been the most frequent cause of cancer-death for over a decade around the world (1). Non-small cell lung cancer (NSCLC) accounts for approximately 80-85% of lung cancers (1-3). Clinical staging of NSCLC is important for prognosis and selection of a treatment strategy. The TNM staging system is considered as the most important tool to determine prognosis and to guide treatment decisions to date (3). However, the TNM staging system provides an incomplete biologic profile of NSCLC and does not always provide a satisfactory explanation for differences in recurrence and survival (4). Clinical variables including TNM staging system, histological type, performance status, and smoking status have been considered prognostic factors in patients with NSCLC (5-7).

F-18 FDG-PET/CT has been well established for the diagnosis and staging in patients with NSCLC. It is also considered as a core investigation in diagnosis of lung cancer, which aids in more accurate staging for lung cancer as confirmed by earlier meta-analysis studies (3, 4, 8, 9). NCCN guideline also recommends F-18 FDG PET/CT scan in operable stage of NSCLC (Stage 1A to IIIA) and that positive nodes on PET/CT scan need pathologic confirmation NCCN guideline (ver 2.2018). However, its relatively low sensitivity to detect brain metastasis on F-18 FDG PET/CT is one of its limitations, as the brain normally use glucose as a metabolite and normal brain parenchyme shows high FDG avidity to reduce the detection of metastatic lesions in brain.

The incidence of occult brain metastasis was once believed to be quite low (10, 11) and not to be cost-effective in routine use of brain MRI in asymptomatic patients with early stage of NSCLC. (4-7). Although preoperative screening of neurologically asymptomatic patients has not been advocated, early detection of silent brain metastasis will alter surgical management and avoid unnecessary thoracotomy (8, 12-16). However, extrathoracic metastatic disease is present in approximately 43% of patients with NSCLC at initial diagnosis and brain is not an uncommon site of metastasis (4, 8). Whereas brain MRI with contrast is the best modality for detecting brain metastases, there is no consensus on its routine initial application in the early stages of lung cancer. National Comprehensive Cancer Network (NCCN guideline ver 2.2018) for the pretreatment evaluation of NSCLC recommends brain MRI with contrast for the stage II and IIIA and optional use of brain MRI in stage IB. (NCCN guideline ver 2.2018) Thus, it may be important to determine the right person who needs to undergo brain MRI study in NSCLC patients with very early T-staging (T1 and T2) at initial diagnosis (17).

The aim of this study was to evaluate an additive role of F-18 FDG PET/CT to predict silent brain metastasis in patients with T1 and T2 adenocarcinoma of lung on chest CT. This study may be the first investigation of metabolic-volumetric parameters on F-18 FDG PET/CT to predict brain metastasis, especially in early stage of lung adenocarcinoma.

II. MATERIALS AND METHODS

Patient Population

A total of 395 neurologically asymptomatic patients with T1 and T2 of lung adenocarcinoma on diagnostic chest CT scans from 2011 to 2014 were consecutively enrolled. All patients underwent chest CT, F-18 FDG-PET/CT and brain MRI with contrast as a part of initial staging. Brain metastasis was determined on initial brain MRI and/or follow up imaging studies up to 6 months. Patient characteristics including smoking history, ECOG performance status and EGFR mutation were collected by medical record reviews. This retrospective study design was approved and informed consent was waived by the Institutional Review Board of Seoul National University Hospital (H-1711-121-901).

Chest CT

Diagnostic CT with contrast was performed using a 120 kV protocol. Axial CT images with slice thickness of 3 mm were transferred to the Picture Archiving Communication System (PACS). TNM-staging (T_{CT}, N_{CT} and M_{CT}) were determined according to the AJCC staging system (AJCC 7_{th} edition). T_{CT} was measured on transaxial images and N_{CT} was considered as positive for mediastinal lymph nodes of larger than 1 cm. M_{CT} were diagnosed as positive when there were suspected metastatic lesions as followings; pleural effusion with or without pleural

nodules, lung nodules of any sizes in different lobes, adrenal nodules of greater than 1 cm, and suspected bone lesions in ribs or spines included on chest CT.

F-18 FDG PET/CT

As initial staging, F-18 FDG PET/CT was performed 1 hour after injection of F-18 FDG (5.18 MBq/Kg) to fasted patients for more than 6 hours (blood sugar level lower than 210 mg/dl). PET/CT imaging was acquired in a three-dimensional acquisition mode (5–6 bed position, 2.5 min/bed) using dedicated PET/CT scanners (Biograph True-Point, Biographm CT 40 and Biographm CT 64; Siemens, Erlangen, Germany). The ordered subsets expectation maximization algorithm with 4 iterations and 8 subsets for the Biograph True-Point scanner and 2 iterations and 21 subsets for the Biograph mCT 40 and 64 scanners was used for image reconstruction, with CT-based attenuation correction.

Image analysis

SUVmax based on body weight and MTV were determined by the attenuation-corrected PET data using volume viewer software (Syngo.Via; Siemens Medical Solution, Knoxville, TN), which provide multiplanar reformatted images. Volumes of interest (VOI) including all the margins of tumors were drawn automatically with

manual modification to define margins around the primary tumor. Peak and mean standardized uptake value (SUVpeak and SUVmean), and total lesion glycolysis (TLG) of primary tumors (T_{PET}) were measured. Among the various threshold methods in determining metabolic volume, fixed SUV thresholds of 2.5 and 40% of maximum voxel count were used for SUVmean and TLG calculations. For the nodal staging (N_{PET}) and extrathoracic metastasis except brain (M_{PET}) on PET/CT, lymph node or distant metastases were determined by visual analysis: discernable or focal FDG avididy compared to mediastinal blood pool activity. After obtaining metabolic-volumetric parameters on F-18 FDG PET/CT, N/M re-staging (N_{CT+PET}, M_{CT+PET}) were determined as positive by combining either CT or PET/CT positive parameters.

Statistical analysis

The values of the PET/CT parameters predictive factors for brain metastasis were evaluated by using Mann-Whitney U test. The correlation between each of the variables was also studied by a Chi-square test. Receiver-operating characteristics (ROC) analysis was performed to evaluate the optimal cutoff value. The method developed by de Long (21) was used to examine difference in the area under the curve (AUC). Logistic regression analysis was done to evaluate metabolic and volumetric as well as clinical parameters to predict brain metastases. Univariate and multivariate analysis were performed by a logistic regression model to identify independent parameters to predict brain metastasis. Explicative variables with P-

value of 0.20 or less by univariate analysis were incorporated in a logistic regression model. When two variables from PET parameters were significantly correlated with each other, the only one variable with the most significantly linked to a risk of brain metastasis was included in the multivariate analysis. Hazard ratio (HRs) and their 95% confidence intervals (CLs) were calculated. All statistical analysis was performed using the Statistical Package for Social Sciences 23.0 statistical software package (SPSS, Inc., Chicago, IL, USA). T, N and M factors by CT and FDG PET were compared each other by NcNemar test. $P<0.05$ was regarded statistically significant.

III. RESULTS

Patient characteristic

A total of 395 patients were enrolled in this study. The median age was 65 years (range, 27-86) and 53% of the patients were female and 47% were men. Fifty-one patients (13%) had brain metastasis on brain MRI; brain metastatic lesions were detected in 43 patients (84%) at initial brain MRI and in 8 patients (16%) during follow up brain imaging within 6 months.

EGFR mutation was present in 229 patients (58%) and smokers or ex-smokers were in 229 (58%). According to the TNM classification by CT scan, T_1 and T_2 stages were 205 (52%) and 190 (48%), N_0 and N_{1-3} stages were 249 (63%) and 146 (37%), M_0 and M_1 disease were 298 (75%) and 97 (25%), respectively. Metasatic disease (M_1 stage) on CT scan were suspected as followings: pleural effusion with or without pleural nodules; 37 (38%), lung nodules in different lobes; 47 (48%), adrenal nodules; 6 (6.0%), and suspected bone lesions in ribs or spines; 7 (7%), respectively. **(Table 1)**

Characteristics of PET parameters (T_{PET}) and N/M-staging

SUVpeak, SUVmean, and TLG, and of the primary tumors in patients with brain metastases were 1.68±0.46, 1.58 ±0.479, and 1.803±0.40, whereas those in patients without brain metastases were 1.37±0.48, 1.32±0.46, and 1.46±0.49,

respectively. All PET parameters above were found to be significantly different between patients with brain metastasis and without brain metastasis by using Mann-Whitney U test ($P<0.05$), as shown in **Table 2.**

In ROC curve analyses, the optimal cut-offs with area under the curve (AUC) were 7.5 with 0.684 in SUVpeak, 4.5 with 0.646 in SUVmean, and 40.5 with 0.718 in TLG, respectively **(Figure 1)**. The sensitivity and specificity of FDG PET for detecting mediastinal lymph node metastases of any node stations were 52.1%, 81.1% and those of CT scan were 23.3% and 92.1%, respectively ($p<0.01$ by McNemar test) **(Table 3)**. PET/CT detected distant metastases in 123 patients, whereas CT did in 97, that is, Extrathoracic distant metastases (M_{PET}) were detected in 26 patients additionally to M_{CT}.

Logistic regression analysis to predict silent brain metastases

In univariate analysis of logistic regression, there were significantly association between the occurrence of brain metastases and primary tumor characteristics on CT and PET. T_{CT} having hazard ratio (HR) of 1.98 ($P=0.027$), while metabolic parameters of primary tumor on FDG PET (T_{PET}), that is SUVpeak, TLG, and SUVmean had HRs of 3.69 ($P<0.001$), 4.71 ($P<0.001$), and 2.95 ($P<0.001$), respectively. Similarly, HRs for N_{CT} and $N_{CT+PET,}$ M_{CT} and M_{CT+PET} were 12.6 ($P<0.01$), 13.5 ($P<0.01$), 11.1 ($P<0.01$), and 57.4 ($P<0.01$), respectively (**Table 4)**.

In multivariate analysis, N_{CT} and M_{CT} staging on CT (HR 5.41; P<0.01, HR1.98; P<0.01) and N_{CT+PET} and M_{CT+PET} staging on PET/CT (HR 3.1; P=0.056, HR37.3; P<0.01) had the independently significant association with the occurrence of brain metastasis, respectively (**Table 5)**.

Comparison of CT and PET parameters to have silent brain metastases according to the M, N and T Factors

Of 395 patients, 51 patients (12.9%) had brain metastasis. The incidences of silent brain metastasis by M_0 vs M_1 on CT, and M_0 vs M_1 on PET/CT were 15 patients (5%) vs 36 (37%) and 3 (1.1%) vs 48 (39%), respectively, which were significantly different (P=0.014) by McNemar test. Similary, those by N_0 vs N_{1-3} on CT and N_0 vs N_{1-3} on PET were 8 patients (3.2%) vs 43 (29.5%) and 4 (2.1%) vs 47 (22.7%), respectively, which were also significantly different (P<0.01). The rate of silent brain metastasis was 6.9% in lower SUVpeak and 20.5% in higher SUVpeak, and 5.2% in lower TLG, 20.4% in higher TLG, and 8.3% in lower SUVmean and 21.2% in higher SUVmean, respectively. Among T-factors on CT and PET/CT, SUVpeak and SUVmean showed statistically significant difference **(Table 6)**. Subsequently, the rate of silent brain metastasis in patients with M_0 and N_0 by PET was 0.6% and that in Stage IIA by PET was 0.5% **(Table 7).**

Table 1. Patients' Characteristics

Characteristics	Number of patients (%) (*n*=395)
Age, median (range)	65 (27-86)
≤ 65	209 (53)
>65	186 (47)
Sex	
Male	184 (47)
Female	211 (53)
Smoking	
Negative	166 (42)
Positive	229 (58)
EGFR mutation	
Negative	166 (42)
Positive	229 (58)
ECOG	
0-2	391 (99)
3-4	4 (0.1)
T stage	
T1	205 (52)
T2	190 (48)
N stage	
N0	249 (63)
N1	23 (5.8)
N2	41 (10.4)
N3	82 (20.8)
M stage *	
M0	298 (75)
M1	97 (25)
Brain metastasis	
Yes	51 (13)
No	344 (87)

ECOG: eastern cooperative oncology group, EGFR: epidermal growth factor receptor; * Brain metastases were not included in M-staging.

Table 2. PET Parameters (T_{PET}) according to the Status of Brain Metastasis

PET parameters	Brain metastasis *n*=51 Mean ± S.D.	No Brain metastasis *n*=344 Mean ± S.D.	AUC	Cut off value	P value
SUVpeak	1.68± 0.46	1.37±0.48	0.684	7.5	0.001
SUVmean	1.58 ±0.479	1.32±0.46	0.646	4.5	0.001
TLG	1.803±0.40	1.46±0.49	0.718	40.5	0.001

SUV; standardized uptake value, TLG; total lesion glycolysis. S.D.; standard deviation

Table 3. Detectability of PET/CT and CT for Mediastinal Lymph Node in T1 and T2 Lung Adenocarcinoma Patients Who Underwent Surgery (n=237)

Modality	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	*P*-value*
PET/CT	38	133	35	31	52.1	81.1	P<0.01
CT	17	151	56	13	23.3	92.1	

*McNemar test, TP; true positive, TN; true negative, FP; false positive, FN; false negative

Table 4. Univariate Regression Analysis of Clinical, CT and PET Parameters to Predict Silent Brain Metastases in Total Patients (n=395)

Factors	Level	No of Patients (BM %)	HR (95% CI)	P-value
Clinical				
Age	≤65	28 (13.4)	0.91 (0.50-1.65)	n.s
	>65	23 (12.4)		
Sex	Male	23 (12.5)	1.07 (0.59-1.93)	n.s
	Female	28 (13.3)		
Smoking	Negative	23 (5.8)	1.75 (0.97-3.16)	n.s
	Positive	28 (7.1)		
EGFR	Negative	26 (6.6)	0.66 (0.36-1.19)	n.s
	Positive	25 (6.3)		
CT+PET				
T_{CT}	T_1	19 (9.3)	1.98 (1.08-3.63)	0.027
	T_2	32 (16.8)		
T_{PET}				
	≤ 7.5	16 (6.9)	3.69 (1.96-6.93)	0.001
SUV_{peak}				
	> 7.5	35 (21.5)		
TLG	≤ 40.5	10 (5.2)	4.71 (2.28-9.17)	0.001
	> 40.5	41 (20.4)		
	≤ 4.5	21 (8.3)	2.95 (1.62-5.40)	0.001
SUV_{mean}				
	> 4.5	30 (21.1)		
N_{CT}	N_0	8 (3.2)	12.6 (5.71-27.68)	0.001
	N_{1-3}	43 (29.5)		
N_{CT+PET}	N_0	4 (2.1)	13.5 (4.76-32.3)	0.001
	N_{1-3}	47 (22.7)		
M_{CT}	M_0	15 (5.1)	11.1 (5.73-21.60)	0.001
	M_1	36 (36.7)		
M_{CT+PET}	M_0	3 (3.1)	57.4 (17.4-189.4)	0.001
	M_1	48 (39)		

EGFR: epidermal growth factor, SUV: standardized uptake value, and TLG: Total Lesion Glycolysis. HR: hazard ratio, CI:confidence interval. * Brain metastases were not included in M-staging, n.s: not significant

Table 5. Multivariate Regression Analysis of Clinical, CT and PET Parameters to Predict Silent Brain Metastases in Total Patients (n=395)

Factors	Level	No of Patients (BM %)	HR (95% CI)
CT			
T_{CT}	T_1	19 (9.3)	1.04 (0.51-2.12)
	T_2	32 (16.8)	
N_{CT}	N_0	8 (3.2)	5.41 (2.60-11.24)
	N_{1-3}	43 (29.5)	
M_{CT}	M_0	15 (5.1)	1.98 (1.50-2.62)
	M_1	36 (5.7)	
CT+PET			
T_{CT}	T_1	19 (9.3)	0.62 (0.27-1.44)
	T_2	32 (16.8)	
T_{PET}			
SUV_{peak}	≤ 7.5	16 (6.9)	1.06 (0.98-1.14)
	> 7.5	35 (21.5)	
TLG	≤ 40.5	10 (5.2)	2.36 (0.92-6.02)
	> 40.5	41 (20.4)	
SUV_{mean}	≤ 4.5	21 (8.3)	2.04 (0.97-4.28)
	> 4.5	30 (21.1)	
N_{CT+PET}	N0	4 (2.1)	3.1 (0.97-9.9)
	N1-3	47 (22.7)	
M_{CT+PET}	M0	3 (3.1)	37.3 (10.8-128.9)
	M1	48 (39)	

SUV: standardized uptake value, and TLG: Total Lesion Glycolysis. BM: Brain metastasis HR: hazard ratio, CI:confidence interval. * Brain metastases were not included in M-staging,≠: One by one among these parameters using logistic regression model for multivariant analysis, n.s: not significant

Table 6. Comparison of CT and PET parameters to Have Silent Brain Metastases according to the M, N and T Factors

Characteristic	Number of patients	No of patients with brain metastases %	Chi-square test	McNemar test
M-factor				
M_0 by CT	298	15 (5.0)	P<0.001	P=0.014
M_1 by CT	97	36 (37.1)		
M_0 by PET	272	3 (1.1)	P<0.001	
M_1 by PET	123	48 (39)		
N-factor				
N_0 by CT	249	8 (3.2)	P<0.001	
$N_+$by CT	146	43 (29.5)		P<0.001
N_0 by PET	188	4 (2.1)	P<0.001	
N_+ by PET	207	47 (22.7)		
T- factor				
T_1 by CT	205	19 (9.3)	P=0.025	
T_2 by CT	190	32 (16.8)		
T1a	83	2 (2.4)	P=0.005	
T1b	121	17 (14.0)		
T2a	146	18 (12.3)	P=0.003	
T2b	45	14 (31.1)		
SUVpeak ≤ **7.**5 by PET	232	16 (6.9)	P<0.01	
SUVpeak >7.5 by PET	163	35 (21.5)		P=0.017
TLG≤ **40.5** by PET	201	10 (5.2)	P<0.001	
TLG> **40.5** by PET	194	41 (20.4)		n.s
2.5SUV_{mean}≤**4.5** by PET	253	21 (8.3)	P<0.001	P<0.001
2.5SUV_{mean}>**4.5** by PET	142	30 (21.2)		
M_0 & N_0 by PET	171	1 (0.6)	n.s	
M_0 & N_0 by CT	216	2 (0.9)		

SUV: standardized uptake value, TLG; Total Lesion Glycolysis, * Brain metastases were not included in M-staging,n.s; not significant

Table 7. Rate of Silent Brain Metastases with respect PET parameters According to the Staging system (AJCC 7th)

Characteristic	Number of patients	No of patients with a brain metastasis %
Stage I or IIA by PET	214	1 (0.5)
Stage I or IIA by CT	227	3 (1.3)
Stage I by PET	163	1 (0.6)
Stage I by CT	201	2 (1.0)
Stage IA by PET	121	1 (0.8)
Stage IA by CT	141	1 (0.7)
Stage IB by PET	42	0
Stage IB by CT	60	1 (1.6)

SUV: standardized uptake value, TLG; Total Lesion Glycolysis,

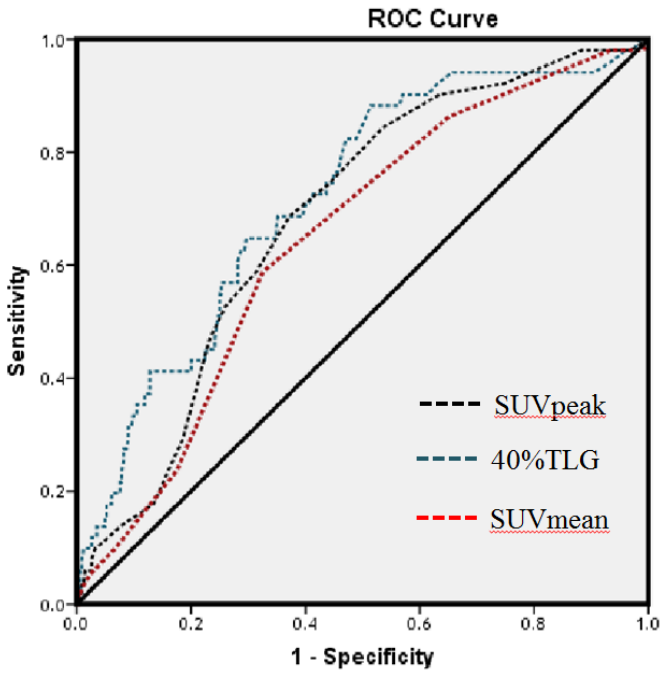

Figure 1. ROC curve analysis of PET parameters of primary tumors to predict brain metastasis

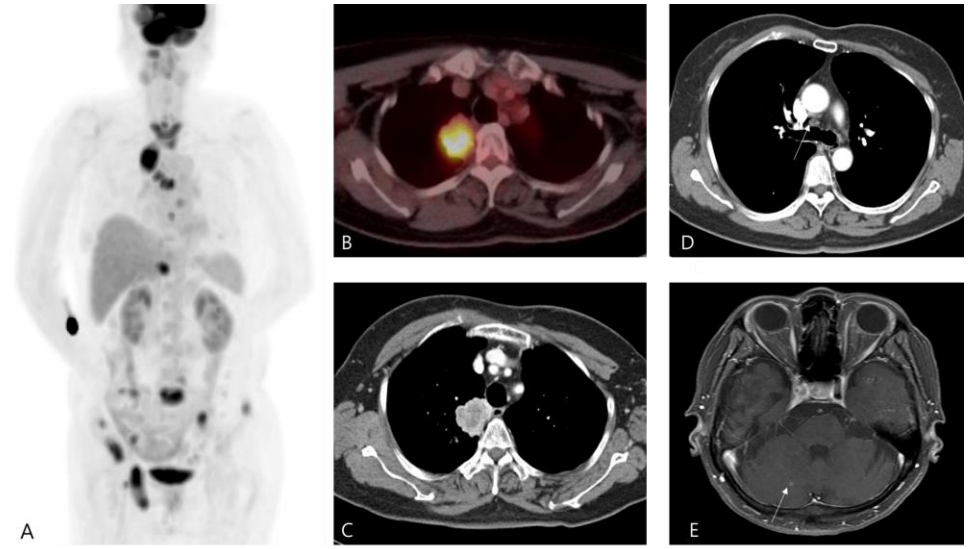

Figure 2. Representative case of extrathoracic metastasis detected on F-18 FDG PET/CT. Sixty five-year-old female patient with right upper lobe lung adenocarcinoma. CT showed 3.4x3.2cm well enhancing mass with central necrosis and enlarged hilar lymph node (stage T_{2a} N_1 M_0). PET/CT demonstrated hypermetabolic mass in the right upper lobe (SUV_{max} 13.5), right hilar lymph node (SUV_{max} 3.5) and multiple hypermetabolic bone lesions in the rib, thoracic vertebra, sacrum, both iliac, right acetabulum, right ischium and right femoral head (stage T_{2a} N_1 M_1). Axial T1-weighted post contrast MRI showed enhanced nodule in the right cerebellum which considered as brain metastasis.

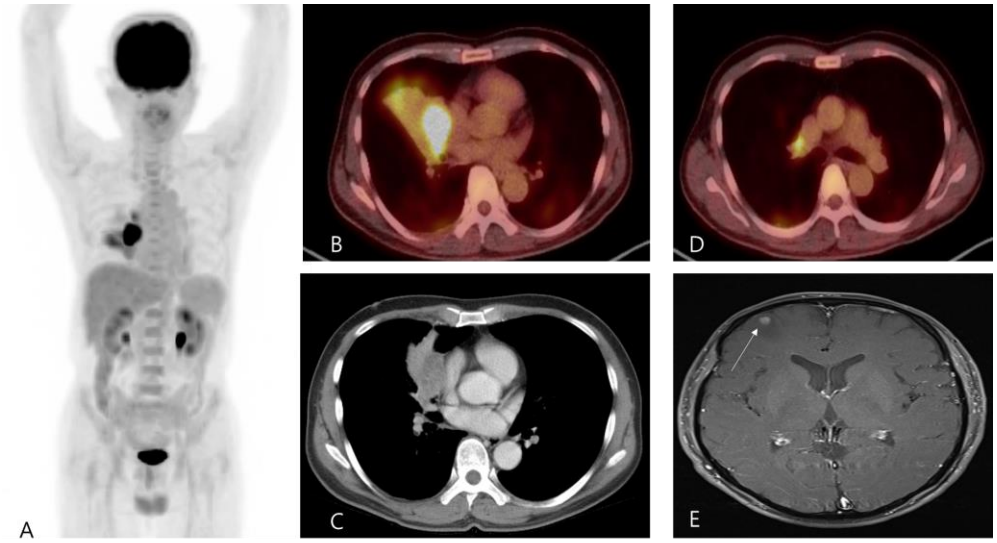

Figure 3. Representative case of additional lymph node detected on F-18 FDG PET/CT. Fifty eight-year-old male patient with right lung adenocarcinoma. Chest computed tomography (CT) showed pulmonary nodule measuring 4.5cm. Also, there is an obstructive lesion with atelectasis in the right medial lobe with no mediastinal lymph nodes metastases; TNM stage (T2a N0 M0). (C). Flurodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) revealed peribronchial hypermetabolic mass in the right medial lobe with maximum standardized uptake value of (SUVmax 17) (A and B). In addition, PET/CT showed FDG uptake of lymph nodes in right hilar and interlobar with SUVmax of 5.4 (D). It was upstaged by PET/CT to (T2a N1 M0) (stage IIA According to the AJCC staging 7th edition). Axial T1-weighted post contrast MRI showed about 8mm enhancing nodule with perilesional edema in right middle frontal subcortical white matter that considered as brain metastasis (E).

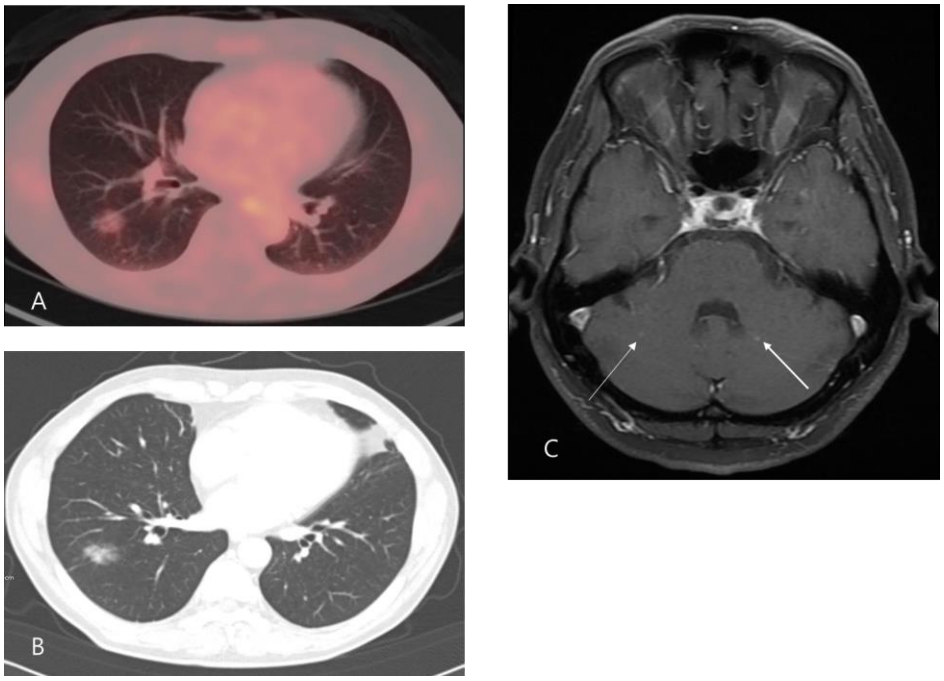

Figure 4. Representative case of a silent brain metastasis in Stage 1A on both chest CT and F-18 FDG PET/CT. A male patient of 64-year old was diagnosed with right lower lobe lung adenocarcinoma. Chest computed tomography (CT) showed pulmonary nodule measuring 2.5cm part solid nodule in the right lung lower lobe with no mediastinal lymph node enlargement (T1b N0 M0) (B). PET/CT demonstrated mild hypermetabolism of the nodule in the right lower lung lobe (SUVmax 1.32) with no other abnormal metabolism (T1b N0 M0) (stage IA; According to the AJCC staging system 7th edition) (A). Axial T1-weighted post contrast MRI showed two tiny enhancing nodules in both cerebellar hemisphere, left one with mild perilesional edema which considered as brain metastasis (C).

IV. DISCUSSION

Staging NSCLC is based on the TNM (tumor, noda involvement, distant metastases) system. In this current study, TNM staging systems on both chest CT and/or F-18 FDG PET/CT were predictable for brain metastasis; T_{CT}, T_{PET}, N_{CT}, N_{CT+PET}, M_{CT}, M_{CT+PET} were associated with high risk of developing brain metastasis in lung adenocarcinoma patients with T1 and T2 stage on chest CT. The finding of brain metastases occurring in 13% of enrolled patients in our data was consistent with the previous reports (18).

One report suggested that T stage might be a risk factor for having brain metastases (8) and another important predicting factor for NSCLC is the nodal status (19). Similarly, results of the Lung Cancer Study Group found that increasing T and N classifications were associated with higher risk of developing brain metastasis (20, 21). PET/CT mainly reflects the metabolic (i.e. SUVpeak) and/or volumetric activity (i.e. SUVmean, TLG) whereas CT does tumor size of primary tumors. In our data, univariate analysis of logistic regression showed significant association between the occurrence of brain metastasis and primary tumor characteristics on PET/CT (T_{PET}), but multivariate analysis did marginal significancy in metabolic-volumetric parameters (SUV mean; p=0.065, TLG; p=0.072), but not in metabolic parameter (i.e. SUVpeak) or T_{CT}. Both of the parameters on CT and PET/CT might have significant associations with silent brain metastasis, however, the predictability of T-parameters would be limited and have marginal significancy in our study group of T1 and T2 lung adenocarcinoma, thus

could not reach an independent significancy. However, association of silent brain metastases with N-staging by CT (N_{CT}) and PET/CT (N_{CT+PET}) were significant both univariate and multivariate regression analysis, even though the significancy of N_{CT+PET} was marginal (p=0.056). Several retrospective and recent meta-analyses have reported that diagnostic accuracy of FDG PET/CT on detecting mediastinal lymph node metastases was more accurate than CT imaging (22). NCCN guideline (ver 2.2018) recommends brain MRI with contrast in stage II and IIIA and optionally in stage IB. In current AJCC staging system (7^{th} edition), lymph node metastases in any N stations reach the stage II and over. Thus, we evaluated diagnostic performance of any N-stations positivity in the enrolled patients who underwent surgery. In current study, the sensitivity and accuracy of any N-station positivity were significant higher in N_{PET} than N_{CT}. The sensitivity and specificity of FDG PET for detecting mediastinal lymph node metastases were 52.1% and 81.1% those of CT scan were 23.3% and 92.1%, respectively. Our multivariate analysis suggests that both of N_{CT} and N_{CT+PET} were more important than T-factors and were identified as having independently association with high risk of developing brain metastasis.

In this current study, HRs to predict silent brain metastasis by intrathoracic M-staging on CT (M_{CT}) and extrathoracic M-staging on FDG PET (M_{CT+PET}) were 11.1 ($P<0.01$) and 57.4 ($P<0.01$), respectively. A significant association of brain metastasis with M_{CT} and M_{CT+PET} staging (M_0 and M_1) were identified as independent predictive factors of high risk in developing brain metastasis. Schrevens *et al.* reported the main additional interest of PET is its ability to detect

metastatic lesions that would have been missed on conventional imaging or are located in clinically hidden or difficult areas, and help in the differentiation of lesions that are equivocal after conventional imaging. Extrathoracic metastases are commonly observed and approximately 40% occur during the diagnosis stage (23, 24). Our data showed about 25% of patients with intrathoracic metastases based on CT images. The brain, liver, adrenal glands, and skeletal system are most likely sites of extrathoracic metastatic diseases as follows; pleural effusion with or without pleural nodules, lung nodules in different lobes, adrenal nodules and suspected bone lesions in ribs or spines defined by intrathoracic metastatic disease in patients with lung cancer (7, 25, 26)

Silent brain metastasis was not uncommon and its incidence rate was more than 1%, even in the early stage of lung adenocarcinoma in our data. Additive roles of F-18 FDG-PET/CT to predict silent brain metastasis in patients with T_1 and T_2 lung adenocarcinoma on chest CT were definitely achieved by detecting extrathoracic metastasis (M_{CT+PET}). N-staging (N_{CT+PET}) and higher metabolic activity (T_{PET}) on F-18 FDG PET also had significant associations with silent brain metastasis, but their additive roles to predict brain metastasis had marginal statistical significances, in this retrospective study **(Figure 2-4)**.

This study has several limitations. Firstly, it was a retrospective, single-center study and the study population who have the silent brain metastasis in patients with stage IB was relatively too small. Even though we extended the population with stage IIA in this current study, there were only 3 patients with silent brain

metastasis, which can lead type II error (false negative finding) in a statistical analysis. Secondly, we did not adopt AJCC staging system 8th edition, but used a 7th edition in this study. Size criteria of T-stage in new edition will have changed quite a lot. Further additional study would be needed by a new size criteria. However, our data with sub-division of size as T1a, T1b, T2a, and T2b did not show significant difference (Table 7). In addition, only one (0.5%) of patients with Stage IIA or Stage I on both CT and FDG PET/CT had a silent brain metastasis, in our data. Thus, the effect of primary tumor size itself may have little difference to our current data (Table 7). Thirdly, we did not confirm all the distant metastatic sites detected on CT or PET/CT. The purpose of this study was to evaluate the predictive value of silent brain metastasis by the imaging parameters on initial diagnostic study, not to evaluate the diagnostic accuracy. Thus, we confirmed the brain metastasis on initial brain MRI with imaging follow-up to 6 months.

V. CONCLUSION

Additive roles of F-18 FDG-PET/CT to predict silent brain metastasis in patients with T_1 and T_2 adenocarcinoma of lung were mainly achieved by detecting extrathoracic metastasis and higher sensitivity of N-staging on FDG PET. In this current study, M_{CT+PET}, N_{CT+PET} and partly metabolic-volumetric parameters of T_{PET} were significantly associated with silent brain metastases in the early T_{1-2} stage. These factors may be used to select the patients who should undergo further brain evaluation of silent brain metastasis, especially in the early stage of lung adenocarcinoma. NCCN guideline (ver 2.2018) optionally recommends brain MRI with contrast in stage IB of non-small cell lung cancer (NSCLS). Further study with a large population of stage I NSCLC and prospective design will be needed to define the additive roles to guide guide optional use of brain MRI study in early stage of NSCLC.

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VII. APPENDIX

Quantitative indexes on F-18 FDG PET/CT

In PET/CT Imaging, the Standardized Uptake Value (SUV) is used for a simple semi-quantitative analysis [16]. The calculation of SUV is performed by pixel wise acquiescent a parametric image, or over a Region of Interest (ROI). The SUV is defined as the ratio of the tissue radioactivity concentration 'c' (e.g. in MBq/kg=kBq/g) at time point't', and the injected activity (e.g., in MBq, extrapolated to the same time t) divided by the body weight 'w' (e.g., in kg) →SUV (t) =c (t)/ {(injected activity) (t)/body weight (w)}.

SUVpeak: is the average of SUV within a small, fixed-size region of interest (ROI peak) centered on a high- uptake part of the tumor. PET Response Criteria in Solid Tumor (PERCIST) recommended SUVpeak taken for the lean body mass.

SUVmean: is much more variable due to operator dependent factors including size and shape of mask delineation and location within or around a lesion, as well as the presence of tumor heterogeneity and variable level of background 18F FDG avidity.

Metabolic tumor volume (MTV): Defined is the volume of tumor tissues with increased FDG uptake and it is a novel index in FDG-PET. Metabolic tumor volume is calculated mostly by visual delineation of tumor edge or side-by-side analysis with contrast-enhanced CT scan.

Total lesion glycolysis (TLG): TLG is another metric that is used in quantifying total tumor burden. It is simply calculated by multiplying the SUVmean by the lesion volume. This is for a single lesion.

국문 초록

조기 폐선암에서 뇌전이에 대한 F-18 FDG 양전자단층촬영술의 추가적 예측능

목적: F-18 FDG PET/CT는 비소세포성 폐암 환자에서 진단 및 병기 검사에 널리 사용된다. 조기 비소세포폐암 환자에서 드물지 않게 뇌 전이가 발생하는데, 상대적으로 낮은 뇌 전이 진단의 민감도는 F-18 FDG PET/CT의 한계 중 하나이다. 이 연구의 목적은 폐 선암 T1과 T2 병기 환자에서 뇌 전이를 예측하기 위한 F-18 FDG PET/CT의 부가적인 역할을 평가하는 것이었다.

방법: 2011년부터 2014년까지 신경학적으로 무증상인 흉부 CT상 T1 및 T2 병기의 폐 선암종 환자 395명을 연속적으로 분석하였다. 모든 환자는 초기 병기 진단의 일부로 흉부 CT, F-18 FDG PET/CT 및 뇌 자기공명영상 (MRI)을 받았다. TNM 병기 (T_{CT}, N_{CT} 및 M_{CT})는 AJCC 병기 결정 시스템 (제 7 판)에 따라 진단 CT 스캔에서 결정되었다. 원발 병소의 표준화된 섭취량(SUV)과 대사체적변수 (T_{PET})를 측정하였고 F-18 FDG PET/CT에서 N/M 병기(N_{CT+PET}, M_{CT+PET})를 결정하였다. 뇌 전이는 초기 뇌 MRI 및 6개월까지의 추적관찰 영상검사에서 확인하였다. EGFR 돌연변이 및 기타 임상 상태는 의무기록을 검토하여 확인했다. 연속 파라미터의 최적 절단값을 평가하기 위해 리시버-오퍼레이팅-캐릭터리스틱 곡선(ROC) 분석을 수행하였다. 폐 선암에서 잠복

뇌전이를 예측하기 위해 임상적 및 PET 대사매개변수를 평가하기 위해 로지스틱 회귀 분석을 수행했다. CT, FDG PET 에 의한 T, N, M 인자를 McNemar 검사로 비교하였다.

결과: 395 명의 환자 중 51 명(13 %)이 뇌 MRI (43 명) 및 추적 이미징 연구 (8 명) 에서 뇌 전이가 진단되었다. F-18 FDG PET 에서의 원발 종양의 대사매개변수(T_{PET})에 대한 뇌 전이를 예측하기 위한 최적 컷오프 및 곡선 하 면적 (AUC)은 SUVpeak, 40%TLG 및 2.5SUVmean 각각에 대해 7.5; 0.684, 40.5; 0.718, 4.5; 0.646 이었다. SUVpeak, 40%TLG, SUVmean 각각에 대한 해당 컷오프 이하에서 뇌전이율은 각각 6.9 %, 5.2 %, 8.3 %였고, cut-off 보다 높은 군에서는 각각 20.5 %, 20.4 %, 21.2 % 이었다(P <0.001). 종격동 림프절 전이에 대한 F-18 FDG PET 의 민감도와 특이도는 각각 52.1%와 81.1%였고 흉부 CT 의 민감도와 특이도는 각각 23.3%와 92.1%였다 (McNemar 검사에서 P<0.01). F-18 FDG PET/CT 는 흉부 CT 에서 진단된 97 건의 흉부 전이 이외에 26 명의 환자에서 뇌를 제외한 123 명의 흉부 외 원격 전이를 검출했다. 단변량 분석에서 FDG PET 의 원발 병소 (T_{PET}), 즉 SUVpeak, 40 % TLG, 2.5SUVmean 의 HR 은 3.69 (P <0.001), 4.71 (P <0.001), 2.95 (P <0.001) 였고, 한편 CT 에 의한 T-병기 분류(T_{CT})는 위험비(HR)가 1.98 (P = 0.027)이었다. CT (N_{CT})와 FDG PET ($N_{CT + PET}$)에 의한 N-staging 의 HR 은 각각 12.6 (P <0.001)과 13.5 (P <0.001)였고, CT 로 평가한 흉부 내 전이 (M_{CT})와 F-18 FDG PET 으로 평가한 흉부 외 전이 ($M_{CT + PET}$) 병기는 각각 11.1 (P

<0.001)과 57.4 (P <0.001)의 HR 을 보였다. 다변량 분석에서, N_{CT} (HR 5.41, P <0.001), M_{CT} (HR 1.98, P <0.001) , $N_{CT + PET}$ (HR 3.1, P = 0.056) 및 $M_{CT + PET}$ (HR37.3, P <0.001)는 각각 뇌 전이의 발생과 유의 한 관련성이 있었다. 뇌 전이의 빈도는 FDG PET/CT 로 병기평가 시 M0 와 N0 에서 0.6%, IIA 이하 병기에서 0.5%였고, 흉부 CT 로 병기평가 시 T1 과 T2 병기의 폐 선암 환자에서 0.9 %와 1.3 %였다.

결론: 잠복 뇌 전이는 드문 일이 아니며 폐 선암의 초기 단계에서도 발병률이 1 %이상이었다. T1 과 T2 병기의 폐 선암 환자에서 F-18 FDG-PET/CT 상 흉곽 외 전이 ($M_{CT + PET}$) 발견이 잠복 뇌 전이를 예측하는데 주요한 추가 역할을 하였다. 이번 후향적 연구에서 F-18 FDG PET 에서의 N-staging (NCT + PET) 및 원발 종양의 높은 대사 활동 정도(T_{PET}) 또한 잠복 뇌 전이와 경계성(borderline) 통계적 유의성을 보였다. NCCN 가이드라인 (ver 2.2018)은 선택적으로 비소 세포 폐암 (NSCLS)의 병기 IB 에서 대조적 인 뇌 조영 MRI 를 권장하고 있다. 원발 종양의 대사 분석과 F-18 FDG PET 의 N 병기 설정의 흉부 CT 보다 높은 민감도는 병기 IB 비소 세포 폐암 환자에서 뇌 MRI 의 선택적 사용을 유도하는 데 도움이 될 수 있다. NSCLC 의 초기 병기에서 뇌 MRI 의 선택적인 사용에 대한 의사결정을 돕기 위해서는 다수의 병기 I NSCLC 환자를 대상으로 하는 전향적 연구가 필요하다.

키워드: 비소세포폐암 (NSCLC), 선암, 뇌 전이, F-18 FDG-PET / CT, 대사 매개 변수

학생 번호: 2016-22150