Bio-Medical Materials and Engineering 24 (2014) 3091–3103
DOI 10.3233/BME-141131
IOS Press

Prognostic value of SUVmax and metabolic tumor volume on 18F-FDG PET/CT in early stage non-small cell lung cancer patients without LN metastasis

Ie Ryung Yoo[1], Soo Kyo Chung[1,*], Hye Lim Park[1], Woo Hee Choi[1], Young Kyoon Kim[2], Kyo Young Lee[3] and Young-Pil Wang[4]
[1]*Department of Radiology, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[2]*Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[3]*Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[4]*Department of Thoracic and Cardiovascular Surgery, College of Medicine, The Catholic University of Korea, Seoul, Korea*

Abstract. This paper aimed to evaluate the prognostic value of maximum standardized uptake value (SUVmax) and metabolic tumor volume (MTV) of the primary tumor on ^{18}F-FDG PET/CT scan in early stage non-small cell cancer (NSCLC) patients without lymph node (LN) metastasis. In the experiment, eighty NSCLC patients pathologically staged as T1N0 or T2N0 were included (M:F=50:30; mean age, 64.8 years). All patients had preoperative ^{18}F-FDG PET/CT scan and curative surgery. FDG uptake in the primary tumor was measured by SUVmax and MTV with various SUV threshold values. SUVmax, MTV of the primary tumor, age, tumor size, histology and differentiation grade were analyzed for association with disease-free survival (DFS). The experimental results showed that the histology types included adenocarcinoma (n=58), squamous cell carcinoma (n=20), and others (n=2); Twenty-two (27.5%) of the 80 patients had a recurrence during follow-up at a median time of 29.1 months; The median SUVmax was 5.26, and the median MTV2.5 was 2.2 cm^3. Univariate analysis showed higher SUVmax (>4), greater MTV (MTV2.5 >4 cm^3), and non-squamous histology were significantly associated with shorter period DFS (p=0.001, p=0.030 and p<0.001). In multivariate analysis, higher SUVmax (p=0.004) and adenocarcinoma histology (p=0.005) were associated with shorter DFS. Therefore, high SUVmax (>4) of the primary tumor on preoperative ^{18}F-FDG PET/CT scan is an independent prognostic factor of shorter DFS in early stage of NSCLC.

Keywords: Non-small-cell lung cancer, PET/CT, standardized uptake value, metabolic tumor volume, early stage

*Corresponding author: Soo Kyo Chung, Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul, 137-701, Korea. Tel.: 82-2-2258-1549; Fax: 82-2-2258-1575; E-mail: iryoo@catholic.ac.kr.

0959-2989/14/$27.50 © 2014 – IOS Press and the authors.

This article is published with Open Access and distributed under the terms of the Creative Commons Attribution and Non-Commercial License.

1. Introduction

Non-small cell lung cancer (NSCLC) is a major medical problem worldwide with high disease-specific mortality rate and poor prognosis. Often patients are diagnosed at advanced stage and curative resection is an option in only about a third of the patients. Multimodality approach is used for treatment of NSCLC, and primary tumor, node, metastasis (TNM) staging is the most important factor of prognosis and determinant of the therapeutic plan. Unless definite risk factor for recurrence such as resection margin involvement is present, observation without adjuvant therapy is chosen for histologically confirmed early NSCLC patients after surgery. However, in a study by Moldvay et al. [1], approximately half of the patients with surgical resection had recurrence, and Naruke et al.'s study showed recurrence in 35% of the stage 1 NSCLC patients [2]. Therefore, TNM staging alone is not a satisfactory prognostic factor, and an accurate prognostic factor that can distinguish early stage patients with higher risk for recurrence could allow selection of patients for post-operative adjuvant chemotherapy or radiation therapy and ultimately improve prognosis.

^{18}F-Fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) utilizes the increased metabolism of cancer cells with high proliferation activity for diagnosis, staging and detection of recurrence in numerous types of malignancy [3,4]. In NSCLC especially, the value of FDG PET/CT for diagnosis and staging has been established after decades of research and clinical experience. Recent interest has grown in the prognostic value of ^{18}F-FDG PET/CT, and previous studies have reported that maximum standardized uptake value (SUVmax) is an independent prognostic factor of NSCLC [5–7]. On the other hand, there have also been studies stating failure to see independent correlation between SUVmax and prognosis [8,9]. Recently, efforts have been made to employ metabolic tumor volume (MTV)–a volumetric, quantitative measurement of tumor cells with high glycolytic activity – for response to chemotherapy or radiation therapy planning [10–13]. A few recent studies showed that the volume-based PET parameter could provide better prognostication than SUVmax alone or tumor size in early-stage NSCLC [12,13]. However, the number of studies on the prognostic value of MTV remains limited and a further validation is necessary.

This study aimed to evaluate whether SUVmax and MTV from pre-operative ^{18}F-FDG PET/CT are independent prognostic factors for recurrence in early NSCLC patients with T stage 1 or 2 and no lymph node metastasis.

2. Materials and methods

2.1. Patients population

This study was conducted in accordance with the regulations of the Institutional Review Board at our hospital, which approved this retrospective study and waived the requirement for informed consent. The population of this retrospective study consisted of 80 patients (50 men, 30 women; mean age, 64.8 years; age range, 42-82 years) with proven NSCLC who had ^{18}F-FDG PET/CT for preoperative staging from February 2004 to August 2009. Patients who received curative surgery with lymph node sampling (lobectomy 75, pneumonectomy 1, sublobar resection 4) and those who confirmed to have T1 or T2 stage by histopathology without LN metastasis were included. TNM staging was based on American Joint Committee on Cancer 7th edition. ^{18}F-FDG PET/CT was performed within less than two weeks before surgery in all patients. The exclusion criteria were: (a) any adjuvant or neoadjuvant chemotherapy or radiotherapy before undergoing PET/CT scan or after operation, (b) underlying lung

disease, such as interstitial lung disease or chronic obstructive pulmonary disease, (c) diabetes mellitus, and (d) pure GGO pattern on CT scan without perceptible FDG uptake.

2.2. ^{18}F-FDG PET/CT

All patients fasted for at least 6 h before the ^{18}F-FDG administration. A dose of 370-555 MBq of FDG was injected intravenously, and scanning began 60 minutes later. None of the patients had blood glucose level greater than 130 mg/dl before the injection. No intravenous contrast agent was administered. Studies were acquired on two combined PET/CT in-line systems (Biographs; Siemens Medical Solutions, Knoxville, Tennessee). The acquisition time was 2-3 minutes per bed position with 40% overlap between two bed positions, and total scan time of PET/CT ranged from 10 to 21 minutes (585 mm of FOV and 162 mm of axial FOV). All patients were in the supine position with their arms being raised during PET/CT scanning. CT began at the orbitomeatal line and progressed to the proximal thigh (130 kVp, 80 mA, 0.8/1/0/1.5 sec of tube rotation time, 1-4 axial pitch size and 5 mm slice thickness; 120 kVp, 50 mA, 0.37/0.5/1.0 sec of tube rotation time, 0.45-2.0 axial pitch size and 5 mm slice thickness; 70cm of FOV). PET scan followed immediately over the same body region. The CT data were used for attenuation correction, and images were reconstructed using a standard ordered-subset expectation maximization (OSEM) algorithm (two iterations, eight subsets; 5 mm in full width at half maximum 3-dimensional Gaussian postfiltering). The axial spatial intrinsic resolution was 6.5 mm or 4.5 mm at the center of the field of view, and data were displayed on a 128 x 128 matrix with a voxel size of 5.3 x 5.3 x 5.3 mm^3 or 168 x 168 matrix with 4.1 x 4.1 x 4.1 mm^3.

2.3. Data analysis

All PET/CT images were reviewed at a workstation with fusion software (Syngo; Siemens Medical Solutions, Knoxville, Tennessee) that provided multiplanar reformatted images and displayed PET images after attenuation correction, CT images and PET/CT fusion images. The images were jointly reviewed for the detection of the primary tumor by two nuclear medicine physicians who had more than eight years of experience. MTV was defined as the summed volume in cubic centimeters (cm^3) of primary cancer, and was measured using a semi-automated contouring program on a Leonardo workstation (Siemens Medical Solutions, Knoxville, Tennessee). As shown in Figure 1 for the measurement of targeted MTV, to define the contouring margin of the primary tumor, authors set various SUV cutoff values including fixed value of 2.5 (MTV2.5), 25% (MTV25), 50% (MTV50) and 75% (MTV75) of the primary tumor SUVmax, and mean SUV (SUVmean) plus two standard deviations (SD) of the liver (MTVliver). Each identified tumor was then segmented semi-automatically in three dimensions. The tumor boundaries were drawn large enough to incorporate target lesions, and in trans axial, coronal and sagittal planes were reduced to eliminate the confounding influence by physiologically glucose-avid tissues such as myocardium. Then, an iso-contour connecting the outline of the target lesion showing cutoff value of SUV was set automatically, and all voxels with SUV over cutoff value within the iso-contour were included in the MTV calculation by the software (Figure 1). After segmentation, the software quantified the final MTV in cubic centimeters. SUVmax of the primary cancer was also measured with VOI. In order to compensate for the difference arising from the two different scanners, correction by mean SUV of liver was used to compute ratio of the tumor to the liver (T/L) [14]. The T/L ratio was calculated as the ratio of tumor SUVmax to mean SUV (SUVmean) of the patient's liver.

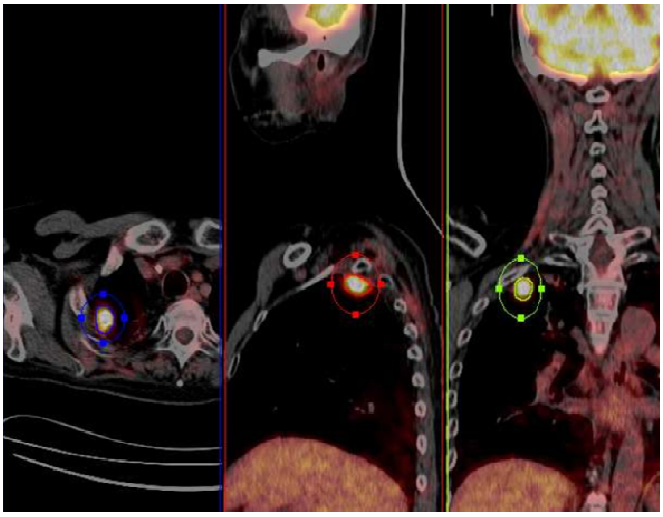


Fig. 1. The measurement of targeted MTV.

2.4. Statistical analysis

All statistical analysis was performed using the SPSS windows 13.0 software (SPSS, Chicago, Illinois). Kaplan-Meier method was used for the estimation of disease free survival (DFS) curves. The time interval for the end point was calculated from the date of operation to the date of recurrence or last clinical follow-up. The minimum P-value approach was used to determine the cutoff value of SUVmax that best dichotomized all patients into two subgroups with poor or good prognosis in terms of DFS. The same method was also used for variable MTV parameters and T/L ratio to determine the cutoff points. As a result, SUVmax of 4, MTV2.5 of 4 cm^3, MTV25 of 10 cm^3, MTV50 of 3 cm^3, MTV75 of 1 cm^3, and MTVliver of 6 cm^3 and T/L ratio of 2 were determined to be the cutoff values respectively, which were used to categorize SUVmax, MTVs and T/L ratio into two subgroups. As two different scanners were used, cutoff values were separately computed for the data set of each scanner and additional analysis was done by dichotomizing each metabolic parameter into the high value and low value groups [6]. Age was also divided into two subgroups by the same method, resulting in 65 years as a cutoff point. Univariate analysis using the log-rank test was used to assess the correlation between DFS and metabolic parameters, clinical and pathologic variables including age, histologic T stage, histologic type, and histologic grade. Cox proportional hazards model using forward conditional stepwise selection was performed for the multivariate analysis with variables that showed statistical significance in the univariate analysis. A p value less than 0.05 was considered significant.

3. Results

3.1. Patients characteristics

The clinical and pathological characteristics of the total 80 patients are summarized in Table 1. The studied group was composed of 50 male and 30 female patients with the mean age of 64.8 years rang

Table 1

Clinical and pathological characteristics of patients (n=80)

Characteristics		No. of patients
Gender		
Male		50
Female		30
Patient age (years)		
Mean		64.8
Range		42-82
Location of primary cancer		
RUL		26
RML		6
RLL		21
LUL		12
LLL		15
Differentiation		
Well		27
Moderate		45
Poor		8
Pathologic T stage		
T1	T1a	28
	T1b	28
T2	T2a	17
	T2b	7
Histology		
Adenocarcinoma		58
Squamous cell carcinoma		20
Others		2
Treatment		
Pneumonectomy		1
Bilobectomy		2
Lobectomy		73
Sublobar resection		4

Others: Pleomorphic carcinoma and large cell carcinoma

ing from 42-82 years, among which 56 patients had pathologic stage T1, and 24 patients had pathologic stage T2. The histologic types were 58 adenocarcinomas (ADC), 20 squamous cell carcinomas (SCC), one large cell carcinoma, and one pleomorphic carcinoma. As shown in Table 2, the median SUVmax was 5.26 with SUVmax ranging from 0.73 to 24.11, and the median values of other metabolic parameters are also listed. Seen from Table 3, twenty-two (27.5%) of the 80 patients had a recurrence, in 27 sites, during the follow-up at a median time of 29.1 months (range 3 ~ 73 months). At the time of the last follow-up, four patients had died due to disease recurrence and one patient had died of another disease. Lung and intra-thoracic LNs were the more common site of recurrence (n=15). Also eight of 27 recurrent sites were extrathoracic (see Table 3). The mean SUVmax for ADC was significantly lower than that for the SCC (4.9±3.7 vs. 9.7±4.5, $p<0.001$). The mean SUVmax of patients with recurrence was significantly higher than that of patients without recurrence (8.7±5.0 vs. 5.3±3.9, $p=0.002$) in all patients. While the mean SUVmax of patients with recurrence was significantly higher than that of patients without recurrence in ADC (7.4±4.9 vs. 3.8±2.6, $p=0.001$), the difference between the mean SUVmax with or without recurrence was not statistically significant in SCC (12.1± 4.5 vs. 9.2± 4.4, $p=0.249$). Recurrence positive cases were seen in 12 T1 and 10 T2 stage patients, in 16 ADC,

Table 2

Median values of metabolic parameters

Parameter		Median	Range
SUVmax		5.26	0.73-24.11
T/L ratio		2.47	0.32-11.48
MTV (cm^3)	MTV2.5	2.2	0.05-376.81
	MTV25	9.91	0.17-272.88
	MTV50	2.59	0.10-151.53
	MTV75	0.64	0.05-55.09
	MTVliver	3.22	0.05-286.86

SUVmax = maximum standardized uptake value
T/L ratio = tumor/liver ratio
MTV = metabolic tumor volume

Table 3

The sites of recurrence

Recurrence site	No.
Lung	9
Intrathoracic lymph nodes	6
Bronchial stump	1
Pleura	3
Extrathoracic lymph nodes	2
Bone	1
Kidney	2
Brain	1
Adrenal gland	1
Liver	1
Total	27

4 SCC, and both the large cell carcinoma and pleomorphic carcinoma cases. Fifteen (68%) of 22 patients showed recurrence within two years.

3.2. Prognostic values

According to the results from the univariate analysis shown in Table 4, patients with lower SUVmax (≤4) showed significantly longer DFS compared with patients with higher SUVmax (>4) (p=0.001). Patients with SUV >4 had a median DFS of 22 months, and patients with SUV ≤4 showed a median DFS of 30 months. Higher T/L ratio (>2), MTV2.5 (>4 cm^3), MTV25 (>10 cm^3), MTV50 (>3 cm^3) and MTV75 (>1 cm^3) were also significantly associated with shorter DFS. Among other clinical and pathologic variables, only histologic type was significantly associated with recurrence (p<0.001) (see Figure 2). The patients with SCC showed better DFS than patients with non squamous histology. In the multivariate analysis, high SUVmax (p=0.004) and ADC histology (p=0.005) were independently correlated with recurrence (see Table 5). This analysis identified the higher SUVmax (Hazard ratio, 19.815; 95% CI, 2.611-150.396) and ADC histology (Hazard ratio, 6.040; 95% CI, 1.699-21.471) of primary cancer as significant independent prognostic factor (see Figures 3 and 4). In the univariate analysis between the high value group and low value group, SUVmax, T/L ratio, MTV50 and histologic type were significantly associated with recurrence. High SUVmax and ADC histology of primary cancer were again significant independent prognostic factors.

Table 4

Univariate analysis by Log-rank test

		Parameter	P value
Age		≤65 vs. >65 yr	0.515
Differentiation		WD, MD, PD	0.845
pT stage		T1 vs. T2	0.061
Histology		SCC, ADC, others	**<0.001***
SUVmax		≤4 vs. >4	**0.001***
T/L ratio		≤2 vs. >2	**0.002***
MTV	MTV2.5	≤4 vs. >4 cm^3	**0.030***
	MTV25	≤10 vs. >10 cm^3	**0.013***
	MTV50	≤3 vs. >3 cm^3	**0.005***
	MTV75	≤1 vs. >1 cm^3	**0.013***
MTVliver		≤6 vs. >6 cm^3	0.095

SUVmax = maximum standardized uptake value
T/L ratio = tumor/liver ratio
MTV = metabolic tumor volume

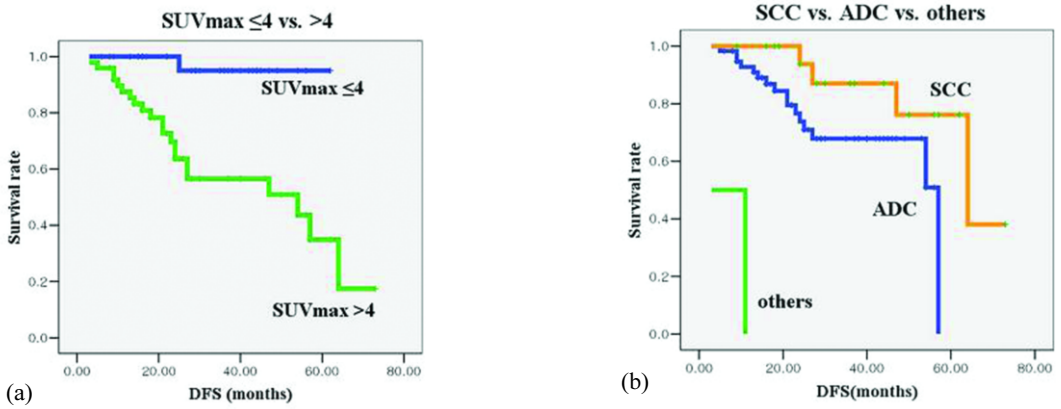


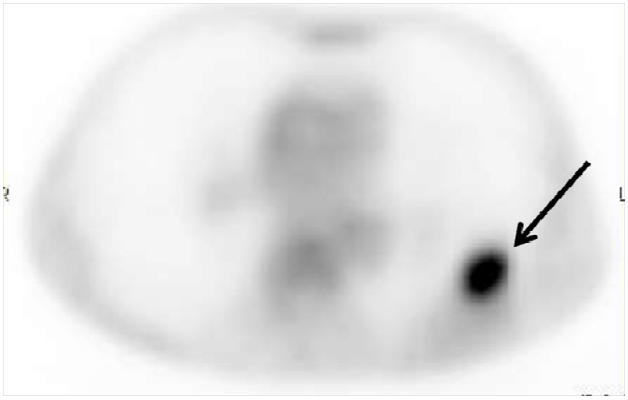
Fig. 2. (a) Kaplan-Meier disease free survival curves of all 80 patients according to SUVmax of primary NSCLC tumor. Curves show clear demarcation of disease free survivals between high SUVmax (>4) and low SUVmax (≤4) groups (p=0.001). (b) Kaplan-Meier disease free survival curves of all 80 patients according to histology types of primary NSCLC tumor. Curves depict significant difference of disease free survivals among histology types (p<0.001).

Table 5

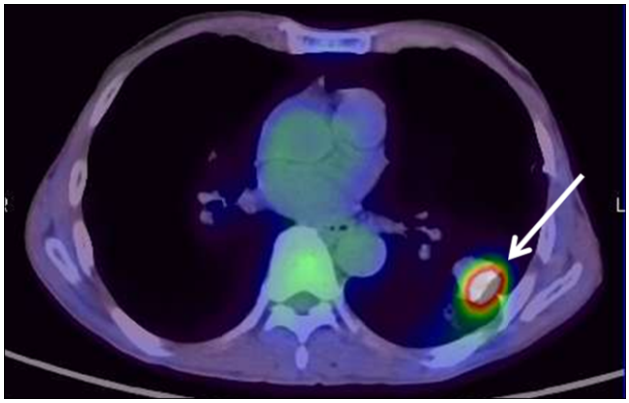
Multivariate analysis by Cox Proportional Hazards Model

Variable	Hazard Ratio	95% CI	P value
SUVmax, ≤4 vs. >4	19.815	2.611-150.396	0.004

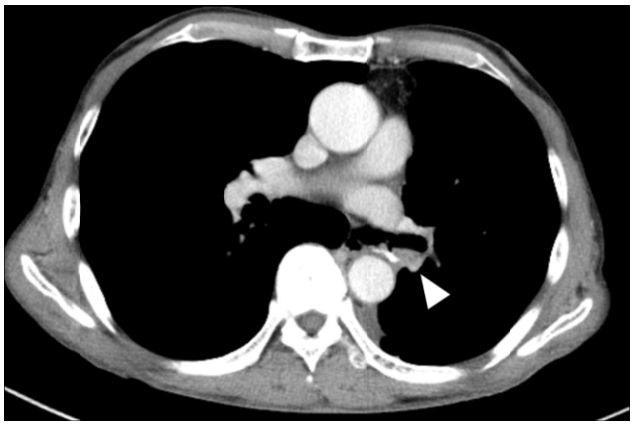
SUVmax = maximum standardized uptake value



(a)

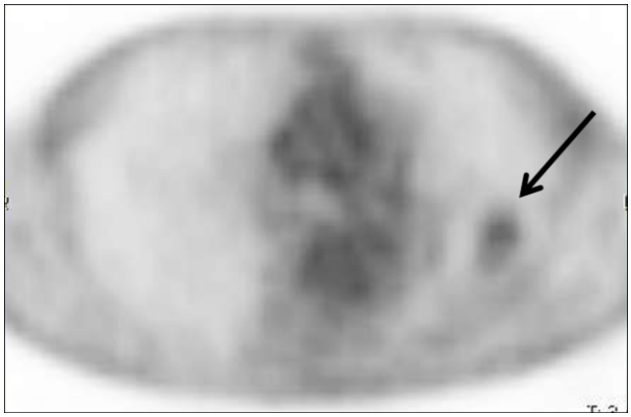


(b)

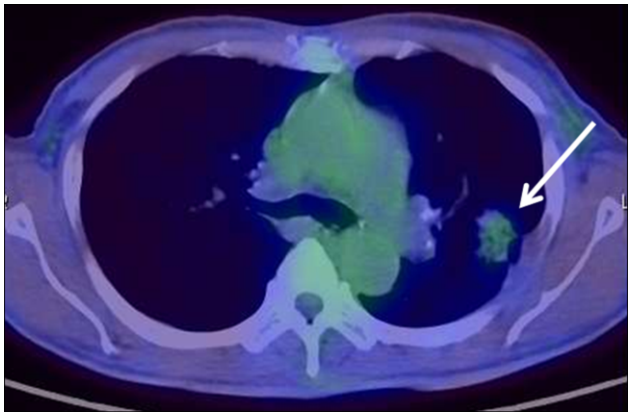


(c)

Fig. 3. Axial PET (a) and PET/CT fusion (b) images of 70-year-old male patient who underwent lobectomy and LN dissection and diagnosed to adenocarcinoma (arrows) of pathologic stage T2aN0 (3.5 x 3.0 cm). The SUVmax of the primary tumor was 6.9. Follow up enhanced CT (c) showed local recurrence in bronchial stump 13 months later (arrowhead). Recurrent tumor was confirmed by bronchoscopic biopsy.



(a)



(b)

Fig. 4. Axial PET (a) and PET/CT fusion (b) images of 57- year-old male patient who underwent lobectomy and LN dissection and diagnosed to adenocarcinoma (arrows) of pathologic stage T1bN0 (3.0 x 2.5 cm). The SUVmax of the primary tumor was 1.5. There was no recurrence with disease free survival of 44 months.

4. Discussion

The principal result of this study is that preoperative SUVmax in primary NSCLC with T1N0 or T2N0 stages has a significant independent prognostic value for recurrence. SUVmax >4 was superior to clinicopathologic factors including histologic T stage and tumor differentiation in predicting recurrence. The result of this study is in keeping with several published literature regarding the significance of pre-operative tumor FDG uptake as prognostic factor in early stage NSCLC [5–7,15–21]. Vansteenkiste et al. [5] reported a SUV of more than 7 to be of significant adverse prognostic importance. Reports by Goodgame et al. [16] and Shiono et al. [17] also stated that FDG PET is a significant independent prognostic factor for recurrence in pathologic stage I patients. Meta-analysis result also demonstrated that the patients with higher SUV have shorter survivals than those with lower SUV [19]. This study has a more homogeneous patient sample than previous studies. To minimize the effect of

TNM stage, which is known to be closely associated with prognosis, only T1 and T2 stage cases without LN metastasis, and patients treated by surgery alone were included.

However, some recent studies reported that FDG uptake in primary NSCLC did not provide additional prognostic value to the pathologic TNM stage. Downey et al. studied 187 resected NSCLC patients and the results showed that although SUV was an independent prognostic factor from clinical TNM stage, SUV didn't add to the prognostic significance of pathologic TNM stage [8]. Vesselle et al. [9] in a study of 208 resected NSCLC patients found SUVmax >7 to be significantly associated with an increased risk of death from NSCLC in univariate analysis. However, in multivariate analysis, SUVmax did not provide significant additional prognostic information over stage and age. These two reports included a greater number of patients compared to previous papers in the literature, or performed multivariate analysis considering numerous variables. In another study by Agarwal et al. [22], the SUVmax was associated with 1.28 fold increases in hazard of death in 363 stage I and II patients, but was not an independent predictor of overall survival. The results of Agarwal's study merit attention as SUVmax was analyzed as a continuous variable and had great statistical power. Thus, to further validate these contrasting results, further studies examining a large number of patients are needed.

For cutoff SUV as a best discriminative value for prognosis, a wide range (5-20) of SUV had been used in many studies [5,7,15,23,24]. In this study, the most discriminative cutoff value of SUVmax was 4, because compared with other studies, only operated T1 and T2 patients were included and a large number of small size tumors were included. The SUV can be underestimated in small tumors with less than 1 or 2 cm in diameter due to partial volume averaging effect. Another reason may be the inclusion of adenocarcinomas with bronchioalveolar carcinoma feature, which are tumors with known low FDG avidity. Furthermore, Ohtsuka et al. [19] reported the optimum cutoff SUVmax of 3.3 for pathologic T1 stage ADC. As seen in the previous reports, the exact definition or setting of the cutoff value that best distinguishes high risk from low risk PET findings varies, which may be due to the large variance in the composition of histologic type and tumor size among the studied populations. In addition, to compare the absolute SUV in multicenter trials and use of different scanners, standardization is a critical issue. In this study, to compensate for the difference that may arise from the two different scanners, different cutoff values were set for each scanner and analyzed by dividing the patients into high value and low value groups. The results of the dichotomized analysis do not differ from the results of setting an absolute SUVmax cutoff point. An accurate cutoff value that can minimize false-positive and false-negative results is necessary, and to reach universal consensus and application in clinical practice, additional studies are necessary. Further studies to possibly set different cutoff values for specific size or pathologic type criteria are also required.

In the current study, 27.5% of patients with T1N0 or T2N0 NSCLC showed tumor recurrence within a median follow-up period of 29.1 months. In operated stage I patients, the reported recurrence rates were 35% [2], 11% [17] and 24% [16], and our recurrence rate did not vary much from these previous studies. The mean SUVmax of patients with recurrence was significantly higher than that of patients without recurrence. When ADC and SCC cases were separately analyzed, the mean SUVmax was significantly different between the recurrence and non-recurrence groups in only the ADC cases. Most of the MTV computations were also different between recurrence and non-recurrence groups in ADC cases. ADC is reported to show lower FDG uptake compared to SCC [25]. In this study, despite the lower mean SUVmax of the ADC cases compared to SCC, the ADC cases had higher recurrent rate. Tumor size is less accurate as a predictive factor for ADC than for SCC. In ADC, even if the primary tumor is tiny in size, there may be extensive metastasis. Thus, even for early stage NSCLC, ADC can show high recurrence rate [26]. The mean SUVmax of the two pathologic types varied considerably

and setting different cutoff values was necessary. The optimal cutoff values showed great difference: 4.2 for ADC and 10 for SCC.

The exact prediction for recurrence is critical in determining the treatment modalities. Especially in the early stage patients, if recurrence risk can be predicted pre-operatively, it will be possible to determine indications for intensity of the preoperative and postoperative treatment. Thus, it will contribute to improving the postoperative prognosis. Also, this study results as well as those in published literature suggest that FDG PET have such a role as a prognostic factor. Currently, among over 160 different factors reported as prognostic factors in NSCLC [27], TNM stage is the most important prognostic factor to date. However, the high recurrence rate of early stage of NSCLC shows that TNM staging alone cannot determine who will or will not benefit from adjuvant therapy. Molecular biology of NSCLC has been extensively explored and many biologic factors responsible for a more aggressive behavior in certain tumors have been discovered. Harpole et al. [28] reported that among stage I NSCLC cancer patients, the 5-year survival was 49% in patients positive for three or more adverse markers of angiogenesis, erbB-2, p53 and Ki-67, while the survival was 81% in patients negative for the adverse marker. Increased proliferating cell nuclear antigen and Ki-67 expression in resected NSCLC patients could also predict poor prognosis and metastasis [29]. In NSCLC, altered glucose metabolism is one example of molecular, biologic derangement, resulting from increased glycolysis, over-expression of glucose transporter protein and increased hexokinase activity. With this principle, ^{18}F-FDG PET is widely used for management of NSCLC and its efficacy is established. ^{18}F-FDG PET can quantify the derangement of glucose metabolism in cancer, using the SUV, a semi-quantitative measurement of FDG uptake. Also, FDG uptake in NSCLC has been correlated with tumor growth rate and proliferation activity. All these findings could explain the relationship between FDG uptake on PET and biologic aggressiveness, in other words, prognosis in NSCLC.

An attempt to measure the tumor volume from CT scan or FDG PET scan has mostly evolved from target volume determination for radiotherapy in lung cancer. MTV is a volumetric parameter of FDG PET/CT and shows good correlation with gross tumor volume (GTV) by CT. Meng et al. reported that SUVmax and MTV of FDG PET/CT in primary NSCLC are positively correlated to microscopic extension related to tumor grade [9]. Since MTV provides information on both tumor burden and tumor aggressiveness, multiple clinical studies are currently in the process to prove the value of volume-based PET parameters in predicting the prognosis of patients with NSCLC. Though the MTV at various threshold values correlated with prognosis in this study, unlike the SUVmax, MTV was not an independent prognostic factor in this study. However, a recent study reported that MTV and total lesion glycolysis was independent prognostic factors for survival in patients of a large population with early stage NSCLC [13]. Therefore, further validation is needed to see if MTV can be used as prognostic value in NSCLC, and to determine which threshold value for computing MTV is most appropriate.

This study has some limitations. First, this study was a retrospective single-institutional study with relatively low statistical power. Second, partial volume correction was not performed though the inclusion of only pathologic T1 and T2 patients meant a large number of cases with small tumor size and thus underestimation of SUVmax from partial volume averaging effect is a possibility. In a study by Goodgame et al. on the prognostic value of FDG PET in resected stage T1 NSCLC, BAC was excluded from the analysis due to its different biological behavior from the large proportion with low FDG uptake [16]. However, it is difficult to make a distinction between the BAC and adenocarcinomas that show different prognosis by pathology or radiologic findings, and only the cases of pure GGO pattern without perceptible FDG uptake, rather than all adenocarcinoma cases with any degree of BAC feature, were excluded. In fact, among the 16 ADC cases positive for recurrence, three cases

initially showed BAC feature on histology. Additionally, small tumor volume could affect the measurement of MTV, resulting in an inaccurate evaluation of the predictive role of smaller MTV. Third, sublobar resections were done in some cases, and lymph node sampling was not performed uniformly in all cases. The prognostic effect of sublobar resection and limited lymph node sampling should be taken into account. Fourth, correlation with other molecular biologic markers such as a proliferation marker was not reviewed or included in the multivariate. Last, lack of standardization of the PET/CT protocol could be a constraint of this study. A prospective study with a larger number of patients is required in the future for further validation of the association between FDG uptake on PET and prognosis in early stage of NSCLC patients, and the standardization of the protocol among studies will also be necessary. In addition, evidence is lack on the value of adjuvant therapy in early stage NSCLC patients at high risk for recurrence, and actual improvement in prognosis from adjuvant therapy also requires validation.

5. Conclusion

FDG uptake in primary NSCLC patients measured by SUVmax on PET has a significant independent prognostic value for recurrence in patients with pathologic stage T1N0 and T2N0. FDG uptake and nonsquamous pathology are superior to other clinicopathologic factors in predicting recurrence in early stage NSCLC patients. In cases with high FDG uptake of NSCLC, adjuvant chemotherapy or radiation therapy may be considered even in early stage patients.

Acknowledgement

The research was supported by the Converging Research Center Program through the Ministry of Science, ICT and Future Planning, Korea (2013K000339).

References

[1] J. Moldvay, P. Scheid, P. Wild, K. Nabil, J. Siat, J. Borrelly et al., Predictive survival markers in patients with surgically resected non-small cell lung carcinoma, Clin. Cancer Res. **6** (2000), 1125–1134.
[2] T. Naruke, T. Goya, R. Tsuchiya and K. Suemasu, Prognosis and survival in resected lung carcinoma based on the new international staging system, J. Thorac. Cardiovasc. Surg. **96** (1988), 440–447.
[3] F.G. Duhaylongsod, V.J. Lowe, E.F. Patz Jr., A.L. Vaughn, R.E. Coleman and W.G. Wolfe, Lung tumor growth correlated with glucose metabolism measured by fluorine-18-fluorodeoxyglucose positron emission tomography, Ann. Thorac. Surg. **60** (1995), 1348–1352.
[4] J.K. Oh, Y.A. Chung, Y.S. Kim, H.M. Jeon, S.H. Kim, T.H. Park et al., Value of F-18 FDG PET/CT in detection and prognostication of isolated extra-axillary lymph node recurrences in postoperative breast cancer, Biomed. Mater. Eng. **24** (2014), 1367–1373.
[5] J.F. Vansteenkiste, S.G. Stroobants, P.J. Dupont, P.R. De Leyn, E.K. Verbeken, G.J. Deneffe et al., Prognostic importance of the standardized uptake value on 18F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: An analysis of 125 cases, J. Clin. Oncol. **17** (1999), 3201–3206.
[6] C. Dooms, A. van Baardwijk, E. Verbeken, R.J. van Suylen, S. Stroobants, D. Ruysscher et al., Association between 18F-fluoro-2-deoxy-D-glucose uptake values and tumor vitality: Prognostic value of positron emission tomography in early-stage non-small cell lung cancer, J. Thorac. Oncol. **4** (2009), 822–828.
[7] S.W. Um, H.J. Kim, W.J. Koh, G.Y. Suh, M.P. Chung, O.J. Kwon et al., Prognostic value of 18F-FDG uptake on positron emission tomography in patients with pathologic stage I non-small cell lung cancer, J. Thorac. Oncol. **4** (2009), 1331–1336.

[8] R.J. Downey, T. Akhurst, M. Gonen, B. Park and V. Rusch, Fluorine-18 fluorodeoxyglucose positron emission tomographic maximal standardized uptake value predicts survival independent of clinical but not pathologic TNM staging of resected non-small cell lung cancer, J. Thorac. Cardiovasc. Surg. **133** (2007), 1419–1427.
[9] H. Vesselle, J.D. Freeman, L. Wiens, J. Stern, H. Nguyen, S. Hawes et al., Fluorodeoxyglucose uptake of primary non-small cell lung cancer at positron emission tomography: new contrary data on prognostic role, Clin. Cancer Res. **13** (2007), 3255–3263.
[10] X. Meng, X. Sun, D. Mu, L. Xing, L. Ma, B. Zhang et al., Noninvasive evaluation of microscopic tumor extensions using standardized uptake vale and metabolic tumor volume in non-small-cell lung cancer, Int. J. Radiat. Oncol. Biol. Phys. **82** (2011), 960–966.
[11] C. Greco, K. Rosenzweig, G.L. Cascini and O. Tamburrini, Current status of PET/CT for tumour volume definition in radiotherapy treatment planning for Non-Small Cell Lung Cancer (NSCLC), Lung Cancer **57** (2007), 125–134.
[12] Y. Lin, W.-Y. Lin, C.-H. Kao, K.-Y. Yen, S.-W. Chen and J.-J. Yeh, Prognostic value of preoperative metabolic tumor volumes on PET-CT in predicting disease-free survival of patients with stage I non-small cell lung cancer, Anticancer Res. **32** (2012), 5087–5092.
[13] S.H. Hyun, J.Y. Choi, K. Kim, J. Kim, Y.M. Shim, S.-W. Um et al., Volume-based parameters of 18F-fluorodeoxyglucose positron emission tomography/computed tomography improve outcome prediction in early-stage non-small cell lung cancer after surgical resection, Ann. Surg. **257** (2013), 364–370.
[14] S. Shiono, M. Abiko, T. Okazaki, M. Chiba, H. Yabuki and T. Sato, Positron emission tomography for predicting recurrence in stage I lung adenocarcinoma: standardized uptake value corrected by mean liver standardized uptake value, Eur. J. Cardiothorac. Surg. **40** (2011), 1165–1169.
[15] K. Higashi, Y. Ueda, Y. Arisaka, T. Sakuma, Y. Nambu, M. Oguchi 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. **43** (2002), 39–45.
[16] B. Goodgame, G.A. Pillot, Z. Yang, J. Shiriki, B.F. Meyers, J. Zoole et al., Prognostic value of preoperative positron emission tomography in resected stage I non-small cell lung cancer, J. Thorac. Oncol. **3** (2008), 130–134.
[17] S. Shiono, M. Abiko and T. Sato, Positron emission tomography/computed tomography and lymphovascular invasion predict recurrence in stage I lung cancers, J. Thoac. Oncol. **6** (2011), 43–47.
[18] R.J. Cerfolio, A.S. Bryant, B. Ohja and A.A. Bartolucci, The maximum standardized uptake values on positron emission tomography of a non-small cell lung cancer predict stage, recurrence, and survival, J. Thorac. Cardiovasc. Surg. **130** (2005), 151–159.
[19] T. Ohtsuka, H. Nomori, K. Watanabe, M. Kaji, T. Naruke, K. Suemasu et al., Prognostic significance of [(18)F] fluorodeoxyglucose uptake on positron emission tomography in patients with pathologic stage I lung adenocarcinoma, Cancer **107** (2006), 2468–2473.
[20] J.C. Chen, T.W. Huang, H. Chang, C. Tzao, W.S. Huang and S.C. Lee, Prognostic value of 18-FDG uptake in early stage NSCLC, Thorac. Cardiov. Surg. **57** (2008), 413–416.
[21] M. Paesmans, T. Berghmans, M. Dusart, C. Garcia, C. Hossein-Foucher, J.J. Lafitte et al., Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer: update of a systematic review and meta-analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project, J. Thorac. Oncol. **5** (2010), 612–619.
[22] M. Agarwal, G. Brahmanday, S.K. Bajaj, K.P. Ravikrishnan and C.Y. Wong, Revisiting the prognostic value of preoperative (18)F-fluoro-2-deoxyglucose ((18)F-FDG) positron emission tomography (PET) in early-stage (I & II) non-small cell lung cancers (NSCLC), Eur. J. Nucl. Med. Mol. Imaging **37** (2010), 691–698.
[23] K. Dhital, C.A. Saunders, P.T. Seed, M.J. O'Doherty and J. Dussek, [(18)F] Fluorodeoxyglucose positron emission tomography and its prognostic value in lung cancer, Eur. J. Cardiothorac. Surg. **18** (2000), 425–428.
[24] V. Ahuja, R.E. Coleman, J. Herndon and E.F. Patz Jr., The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with nonsmall cell lung carcinoma, Cancer **83** (1998), 918–924.
[25] R.J. Downey, T. Akhurst, M. Gonen, A. Vincent, M.S. Bains, S. Larson et al., Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection, J. Clin. Oncol. **22** (2004) 3255–3260.
[26] K. Higashi, Y. Ueda, K. Ayabe, A. Sakurai, H. Seki, Y. Nambu et al., FDG PET in the evaluation of the aggressiveness of pulmonary adenocarcinoma: correlation with histopathological features, Nucl. Med. Commun. **21** (2000), 707–714.
[27] C. Li, H. Li, K. Jiang, J. Li and X. Gai, TLR4 signaling pathway in mouse Lewis lung cancer cells promotes the expression of TGF-ß1 and IL-10 and tumor cell migration, Biomed. Mater. Eng. **24** (2014), 869–875.
[28] D.H. Harpole Jr., W.G. Richards, J.E. Herndon II and D.J. Sugarbaker, Angiogenesis and molecular biologic substaging in patients with stage I non-small cell lung cancer, Ann. Thorac. Surg. **61** (1996), 1470–1476.
[29] A.M. Lavezzi, L. Santambrogio, N. Bellaviti, B. Biondo, M. Nosotti, F. Radice et al., Prognostic significance of different biomarkers in non-small cell lung cancer, Oncol. Rep. **6** (1999), 819–825.