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Prediction of survival and cancer recurrence using F-18 FDG PET/CT in patients with surgically resected early stage (Stage I and II) non-small cell lung cancer

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The aim of the current study was to investigate the prognostic value of SUV_{max} in patients with completely resected early stage (stage I & II) NSCLC.

A retrospective review identified 76 patients with surgically resected early (stage I and II) NSCLC who received F-18 FDG PET/CT at diagnosis of cancer. Survival analysis was conducted using Kaplan-Meier analysis, and survival curves stratified by age, sex, mediastinal lymph node involvement, SUV_{max}, and TNM staging were generated for estimation of overall survival and disease free survival (DFS). Independent predictive factors for survival were determined using Cox proportional hazard model.

For overall survival, the median survival of the patients with tumor $SUV_{max} \leq 6.7$ was 48.9 months and was significantly longer than the patients with tumor $SUV_{max} > 6.7$ (Log rank test, $X^2=18.01$, $p<0.0001$). The overall DFS was better in patients with tumor $SUV_{max} \leq 5.9$ than the patients with tumor $SUV_{max} > 5.9$. The median survival of the patients with tumor $SUV_{max} \leq 5.9$ was 31.7 months (Log rank test, $X^2=16$, $p=0.0001$).

In conclusion, high FDG uptake measured by F-18 FDG PET/CT might have a prognostic value for overall survival and DFS in surgically resected early stage (stage I & II) NSCLC even after stratified by pathologic stages.

Key words: F-18 FDG, Early stage, non-small cell lung cancer, overall survival, disease free survival

Lung cancer is leading cause of cancer-related death in the United States. In the United States, approximately 215,020 new cases of lung cancer are diagnosed each year; the estimated deaths were 161,840 in 2008 [1].

Traditionally, early stage non-small cell lung cancer (NSCLC) is managed with surgical resection. In contrast to locally advanced and metastatic NSCLC, the prognosis following resection for early stage disease is favorable. In a number of reports, 5 year survival rates for patients with stage I disease range 60~75 %, while for stage II disease five-year survival rates vary from 36~60 % [2-6]. However, the recurrence rate after curative resection still remains high and approximately half of the patients may relapse and die within 5 years, and majority of these relapses are due to distant metastasis and occur within 2 years after complete resection [7, 8].

Fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET) has been established as a standard imaging technique in staging, treatment monitoring, prediction of survival after treatment, and follow-up of NSCLC patients [9-15]. Maximal standardized uptake value (SUV_{max}) measured by F-18 FDG PET is a semiquantitative index reflecting tumor metabolism and activities.

Several previous studies suggested the prognostic role of F-18 FDG PET in patients with early stage NSCLC after complete resection [16-20]. Although different threshold SUV_{max} values were proposed, high FDG uptake is associated with reduced overall survival and disease-free survival of patients with completely resected early stage NSCLC.

In the current study, we investigated the prognostic value of SUV_{max} measured by preoperative F-18 FDG PET in patients with completely resected early stage (stage I & II) NSCLC.

Materials and methods

Patient eligibility. Retrospectively, we reviewed lung cancer registry at our institution and identified early stage NSCLC (stage I and II) based on histologic examinations of resected specimens between 2005 and 2009. Patients were excluded from the current study if they had received neoadjuvant or adjuvant chemotherapy or radiation treatment, had any previous lung cancer, multiple primary cancer. Seventy six patients met these inclusion and exclusion criteria. All 76 patients underwent preoperative F-18 FDG PET/CT, computed tomography (CT), brain magnetic resonance imaging (MRI), and bone scan. This study was approved by our institutional review board and written informed consent was obtained from each patient.

Clinical follow-up and End point assessment. During the follow-up, complete physical examination, chest CT, routine laboratory test were performed every 6 months. Recurrence was defined as any appearing of new cancer focus in a disease-free patient. The time interval between the surgery and cancer recurrence were determined. The duration of disease-free survival (DFS) was calculated as the time interval between the surgery date and date of the cancer recurrence, death without evidence of recurrence, or the last clinical contact. The follow-up was completed by 30th, April 2010.

F-18 FDG PET/CT. F-18 FDG PET/CT image was done with a dedicated PET/CT scanner (Gemini, Philips, Milpitas, CA, USA), consisting of a dedicated germanium oxyorthosilicate full-ring PET scanner and a dual slice helical CT scanner. Standard patient preparation included at least 8 hours fasting and a serum glucose level of less than 120 mg/dL before F-18 FDG administration (mean dose, 383.7±47.4 MBq; range, 314.5~488.4 MBq). PET/CT imaging was performed 60 minutes after injection of F-18 FDG. At 60 minutes after administration of F-18 FDG, low-dose CT (30 mAs, 120kV) covering area from the base of the skull to the proximal thighs was performed for the purpose of attenuation correction and precise anatomical localization. Thereafter, emission scan was conducted in the 3-dimensional mode. Emission scan time per bed position was 3 minutes; 9 bed positions were acquired. To calculate maximal standardized uptake values (SUV_{max}), manually defined circular regions of interest (ROI) were drawn on the attenuation corrected emission images throughout axial planes in which a suspicious lesion could be delineated.

Statistical analysis. All numerical data was expressed as mean±SD. Survival analysis was conducted using Kaplan-Meier analysis, and survival curves stratified by age, sex, mediastinal lymph node involvement, SUV_{max}, and TNM staging were generated. Log rank test was used to compare the survival between each group. Overall survival was measured from the date of surgery to the date of death or most recent follow-up. Also, disease free survival (DFS) was measured from the time of surgery to the date of first recurrence of NSCLC. Independent predictive factors for survival were determined using Cox proportional hazard model. Receiver operating characteristic curve (ROC) analysis was performed for the prediction of survival after treatment using quantitative indices of F-18 FDG PET/CT. Data analyses were conducted with MedCalc. Statistical significance was defined as $P<0.05$.

Table 1. Clinico-pathological characteristics of the study population.

	Variables	Number of patients	%
Sex (Male/Female)		48/28	
Mean age		64.2 years (26	
Pathology	Adenocarcinoma	36	47.4
	SCC	24	31.6
	Others	16	21
T stage	T1a	18	23.7
	T1b	15	19.7
	T2a	31	40.8
	T2b	5	6.6
	T3	7	9.2
N stage	N0	60	78.9
	N1	16	21.1
Stage	Ia	30	39.5
	Ib	20	26.3
	IIa	18	23.7
	IIb	8	10.5
Operation	Segmentectomy	5	6.6
	Lobectomy	65	85.5
	Bilobectomy	2	2.6
	Pneumonectomy	4	5.3

Results

Patient characteristics and follow-up. The characteristics of the patients are given in Table 1. Forty-eight patients were male (63.2%) The mean age at the time of diagnosis was 64.2 years (range, 26~81 years). Thirty-six patients had adenocarcinoma and 24 patients had squamous cell carcinoma. The median follow-up time was overall 30.8 month (range, 0.9~59.1 month), for surviving patients 31.3 month (range, 3.2~59.1 month), and for deceased patients 15.3 month (range, 0.9~48.9 month).

Exploring a cutoff point of the SUV_{max}. The optimal cutoff values of SUV_{max} for estimation of death and cancer recurrence was calculated. For overall survival, SUV_{max} >6.7 was chosen (area under curve (AUC), 0.890; standard error, 0.0489; 95% confidence interval (CI), 0.798~0.951; p=0.0001). For disease free survival, SUV_{max} >5.9 was chosen (AUC, 0.775, standard error, 0.0592; 95% CI, 0.665~0.863, p=0.0001).

Overall survival. Figure 1 demonstrates the Kaplan-Meier survival curves of the two groups of patients with SUV_{max}>6.7 or SUV_{max}≤6.7. Six patients (27.3%) with a tumor SUV_{max}>6.7 and none of patients with tumor SUV_{max} ≤6.7 died during follow-up period. The median survival of the patients with tumor SUV_{max}≤6.7 was 48.9 months and was significantly

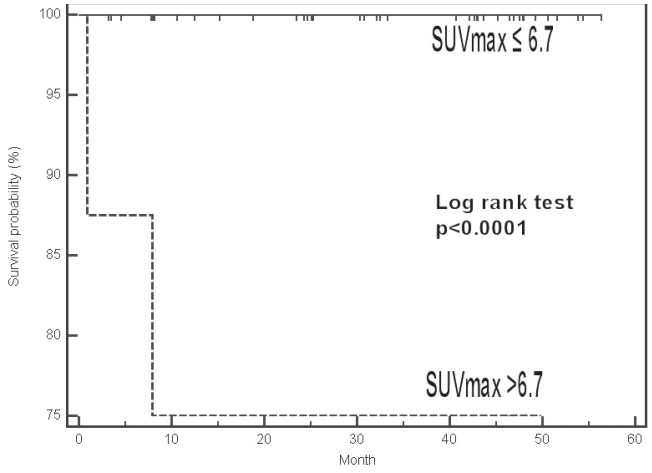


Figure 1. Kaplan-Meier overall survival curve of entire study cohort.

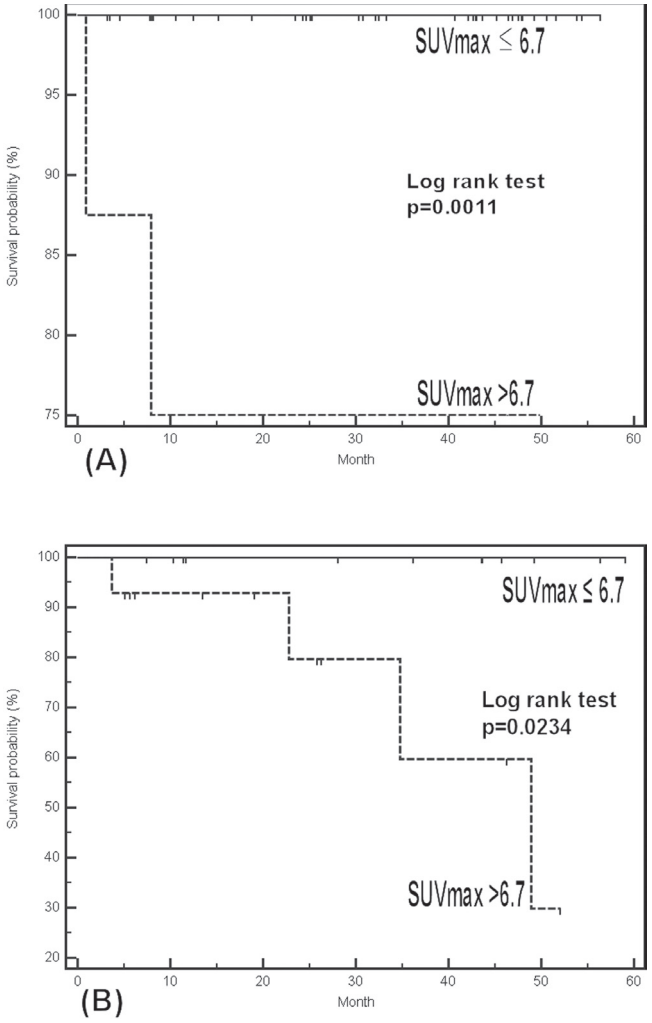


Figure 2. Kaplan-Meier overall survival curve of subgroup analysis stratified by pathologic stages (A; stage I, B; stage II).

greater than the patients with tumor SUV_{max}>6.7 (Log rank test, X^2=18.01, p<0.0001).

Subgroup analysis was performed according to the pathologic stage of the patients. For stage I patients (n=50), the survival was significantly better in patients with tumor SUV_{max}≤6.7 than the patients with tumor SUV_{max}>6.7 as shown in Figure 2A (Log rank test, X^2=10.6, p=0.0011). For stage II patients (n=26), the survival was also significantly better in patients with tumor SUV_{max}≤6.7 than the patients with tumor SUV_{max}>6.7 (median survival, 48.9 month) as shown in Figure 2B (Log rank test, X^2=5.13, p=0.0234).

Disease free survival. During the follow up, the recurrence was found in 5 patients (6.6%) in group with tumor SUV_{max}≤5.9 and in 17 patients (22.4%) in group with tumor SUV_{max}>5.9. As shown in figure 3, the overall DFS was better in patients with tumor SUV_{max}≤5.9 than the patients with tumor SUV_{max}>5.9. The median survival of the patients with tumor SUV_{max}≤5.9 was 31.7 months (Log rank test, X^2=16, p=0.0001).

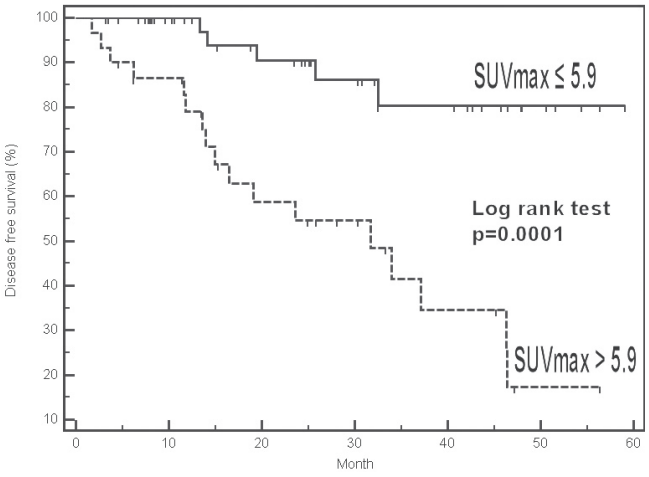
For stage I patients (n=50), the survival was significantly better in patients with tumor SUV_{max}≤5.9 than the patients with tumor SUV_{max}>5.9 (median survival, 34 month) as shown in Figure 4A (Log rank test, X^2=6.99, p=0.0082). For stage II patients (n=26), the survival was also significantly better in patients with tumor SUV_{max}≤6.7 than the patients with tumor SUV_{max}>6.7 (median survival, 16.5 month) as shown in Figure 4B (Log rank test, X^2=4.09, p=0.0431).

Prediction of overall survival and DFS. Table 2 shows the univariate and multivariate analyses for the prediction of overall survival and DFS of the entire cohort. Cox proportional hazard regression analysis reveals that the SUV_{max} was the potent predictor of overall survival. In order to define the prognostic factors for DFS, multivariate survival analysis was performed using Cox proportional hazard model. As shown in Table 2, the potent predictor of DFS was also SUV_{max}.

Discussion

The current study revealed that F-18 FDG PET/CT could predict tumor recurrence and survival in surgically resected early stage (stage I & II) NSCLC. Also, F-18 FDG PET/CT could predict prognosis of early stage NSCLC even stratified by pathologic stages. Among various variables, the SUV_{max} of primary tumor was the most potent predictor of overall survival and DFS in the early stage NSCLC patients.

A recent systematic review identified 9 studies that examined FDG uptake and prognosis in patients with surgically treated stage I NSCLC [21]. Although significant heterogeneity existed across 9 studies included in their review, they found substantial evidence that the degree of FDG uptake in the primary tumor is associated with prognosis in surgically resected stage I NSCLC [21].



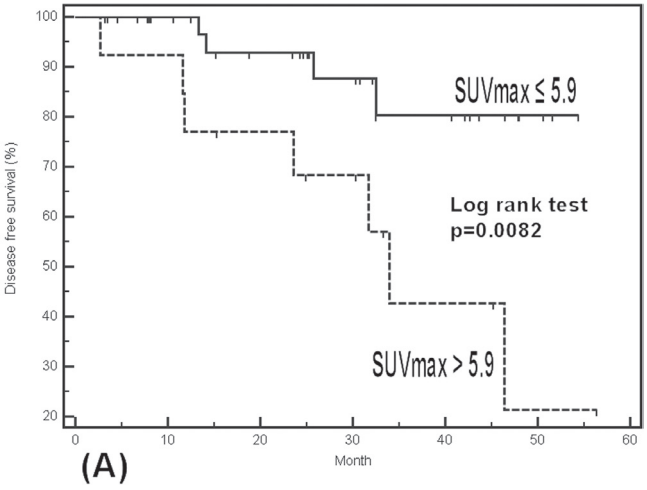


Figure 3. DFS analysis of entire cohort

On the contrary to the current study, the majority of previous studies regarding the prognostic role of F-18 FDG PET in early stage NSCLC recruited stage I patients for reasons of study homogeneity [17-19, 21, 22]. Most of these studies evaluated SUV_{max} in primary tumor before treatment and they founded that FDG uptake in primary tumor could predict overall survival and tumor recurrence with different thresholds of SUV_{max}.

Interestingly, a recent study conducted the prognostic role of F-18 FDG PET in homogenous stage I adenocarcinoma patients concluded that patients with higher preoperative SUV_{max} values have significantly higher recurrence rates [19]. They insisted that even in stage I adenocarcinoma patients, mass size and SUV_{max} are related to higher rates of recurrence, and thus, these patients require more attentive observation after curative resection [19]. The great strength of their study is that, to control for potential bias due to stage and histology,

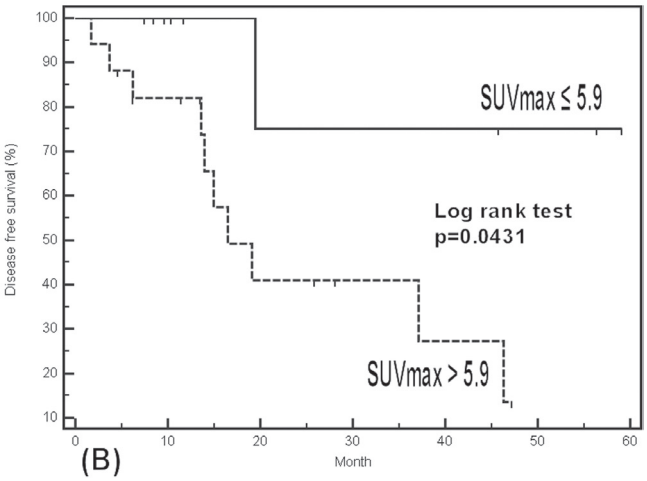


Figure 4. Comparison of Kaplan-Meier DFS curve of pathologic stage I and II (A; stage I, B; stage II).

Table 2. Overall survival and Disease free survival analyses.

	Overall survival				DFS			
	UA	Multivariate analysis			UA	Multivariate analysis		
	p value	HR	95% CI	p value	p value	HR	95% CI	p value
Age (>65)	0.8938	0.64	0.08~4.70	0.6404	0.1511	0.45	0.17~1.18	0.1087
Sex (male)	0.3871	0.80	0.05~12.8	0.8784	0.1534	0.57	0.18~1.80	0.3421
Size (>2 cm)	0.6119	0.70	0.08~5.87	0.7454	0.7261	1.87	0.60~5.81	0.2756
LN (+)	0.0082	-	-	-	0.1511	0.31	0.07~1.39	0.1309
Stage	0.0918	-	-	-	0.0184	3.09	0.87~10.9	0.0805
SUV_{max} (>5.9)	-	-	-	-	0.0001	1.23	1.06~1.44	0.0064
SUV_{max} (>6.7)	<0.0001	1.48	1.09~2.02	0.0118	-	-	-	-

CI; Confidence interval
HR; Hazard ratio
UA; Univariate analysis

the subjects were confined the pathologically proven stage I adenocarcinoma.

Similar to the current study, Hanin et al [16] studied the prognostic value of PET FDG in patients with completely resected 96 NSCLC patients with stage I & II. They found that high FDG uptake (SUV_{max}>7.8) is associated with reduced overall survival and DFS of patients with completely resected stage I–II NSCLC. Subgroup analyses according to the pathologic stages of their study cohort found that F-18 FDG PET could predict overall survival and DFS in patients with stage I but not in stage II NSCLC, which is different finding compared to the current study.

According to another interesting study by Dooms et al [20], SUV_{max} and partial volume corrected SUV_{max} (PVC SUV_{max}) were associated with an increased risk of death in univariate analysis. However, after correcting for stage, tumor size, and age in multivariate analysis, only PVC SUV_{max} was the potent predictor of the survival in their study. In their study, why the PVC SUV_{max} was potent predictor of prognosis could be explained by high Ki-67 and high CAIX length density by multivariate logistic regression analysis.

However, a recent study reported limited prognostic value of SUV_{max} in early stage (stage I & II) NSCLC [23]. They found that each doubling of SUV_{max} as determined by preoperative PET is associated with a 1.28-fold increase in hazard of death in early-stage (I & II) NSCLC. However, they noted that preoperative SUV_{max} is not an independent predictor of overall survival. Similar disappointing result was also noted in advanced NSCLC. Why the SUVmax of the primary tumor could not be prognostic factor may be explained by various factors such as dichotomized age, absence of multivariate analysis, excluding age factor and tumor size in multivariate analysis, and small size of the primary tumor [23]. However, in the current, after considering of all these confounding factors, the SUV_{max} was the most potent predictor of overall survival and DFS in surgically resected early stage NSCLC even after stratified by pathologic stages.

A number of previous studies have tried to set optimal SUV_{max} cut-off values to predict patient`s prognosis in early stage NSCLC with different values of SUV_{max} [16~22]. In the current study, the optimal cut-off values of SUV_{max} for prediction of overall were 6.7 and 5.9 for DFS. Previous several studies set the same SUVmax for estimation of overall survival and DFS [16~22]. The only one value of SUV_{max} might not suitable for prediction of different nature of overall survival and DSF done in previous studies. In the current study, we used different values of SUV_{max} for prediction of overall survival and DFS in entire study cohort and subgroups stratified by pathologic stages. This kind of analysis could strengthen the prognostic value of SUV_{max} in early stage NSCLC for estimation prognosis.

Some limitations of current study should be considered. First, the current study was the retrospective analysis of early stage NSCLC. Second, as previously reported [23], we could not set the tumor stage specific optimal cut-off values of SUV_{max} because of relatively small population of pathologic stage II patients.

In conclusion, high FDG uptake measured by F-18 FDG PET/CT might have a prognostic value for overall survival and DFS in surgically resected early stage (stage I & II) NSCLC even after stratified by pathologic stages.

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