

Prognostic stratification using F-18 FDG PET/CT in patients with advanced stage (Stage III and IV) non-small cell lung cancer

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F-18 FDG PET could provide prognostic information in patients with advanced resectable NSCLC. In the current study, we investigated the prognostic implication of F-18 FDG PET after chemotherapy in patients with advanced stage III and IV NSCLC.

A retrospective review identified 19 patients with advanced stage (stage III and IV) NSCLC who received F-18 FDG PET/CT at diagnosis of cancer and after chemotherapy. The visual response and changes of SUV max before and after treatment on survival was investigated using Kaplan-Meier and Cox proportional hazard regression analyses.

The median follow-up time was overall 24.8 month (range, 9.4~59.8 month), for surviving patients 41 month (range, 34.1~59.8 month), and for deceased patients 16.6 month (range, 9.4~29.4 month). Overall survival after baseline F-18 FDG PET/CT at 1 year was 73.7% and at 2 year was 47.4%. Comparing patients with and without F-18 FDG PET/CT response, there was statistically significant difference in overall survival between the 2 groups (median survival time, responder, 29.4 month; non-responder, 14.2 month, $X^2=3.91$, $p=0.048$). Also, using the $\% \Delta \text{SUV}_{\text{max}}$ for the comparison, significant difference was existed in overall survival between 2 groups ($X^2=12.6$, $p=0.0004$). When the tumor reveals more than 17.85% reduction of $\% \Delta \text{SUV}_{\text{max}}$, the survival could be predicted (AUC, 0.857; standard error, 0.0866; 95% confidence interval, 0.622~0.971; sensitivity, 75%; specificity, 100%; $p=0.0001$). With Cox proportional hazard model, $\% \Delta \text{SUV}_{\text{max}}$ was determined to be a potent prognostic factor for survival (X^2 , 12.09; $p=0.0005$).

In conclusion, using the visual and quantitative analyses of F-18 FDG PET/CT, the responder to chemotherapy in advanced stage NSCLC patients had a better prognosis. Moreover, the potent predictor of prognosis in advanced stage NSCLC patients was $\% \Delta \text{SUV}_{\text{max}}$.

Key words: Non-small cell lung cancer, F-18 FDG PET/CT, survival, chemotherapy

Lung cancer is leading cause of cancer-related death in the United States (1). 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].

At the time of initial diagnosis the majority of patients with non-small cell lung cancer (NSCLC) present locally advanced or metastatic lesions. The overall 5-year survival rate is less than 9% in those patients [2]. For those patients, an acceptable treatment consists of a combination of chemotherapy and radiotherapy and tumor response after induction chemotherapy may be an important prognostic marker for survival [3].

Fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET) has been established as a standard imaging modality in staging/evaluation, treatment, and fol-

low-up of lung cancer patients [4]. Also, F-18 FDG PET has a significant role for prediction of survival after various treatments in patients with NSCLC [3, 5–9].

Assessment of tumor response after treatment is a crucial step for determination of prognosis and treatment regimen in cancer patients. Traditionally, morphologic imaging modalities had been used in the tumor response evaluation. However, morphologic imaging modalities have limitations in differentiating necrotic tumor or fibrotic tissue from residual tumor tissue [10]. Metabolic tumor response using F-18 FDG PET after chemotherapy has a significant correlation with survival in NSCLC [11]. Moreover, metabolic tumor response is more accurate in early assessment of tumor response to treatment of NSCLC than structural imaging modalities.

Some studies have shown that F-18 FDG PET could provide prognostic information in patients with advanced resectable NSCLC [5, 8]. However, it is unclear whether the F-18 FDG PET could provide prognostic information after palliative chemotherapy in patients with stage III and IV NSCLC. In the current study, we investigated the prognostic implication of F-18 FDG PET after chemotherapy in patients with advanced stage III and IV NSCLC.

Materials and methods

Patient eligibility. This study was approved by our institutional review board and written informed consent was obtained from each patient. Retrospectively, we reviewed lung cancer registry at our institution and identified advanced stage NSCLC (stage III and IV) between 2005 and 2006. All 30 patients were identified and required to have undergone F-18 FDG PET/CT and computed tomography (CT) at the time of establishing a pathologic diagnosis without any treatment and to have had at least 3 months of follow-up. For the final analysis, 11 patients were excluded from subsequent study. Five patients did not undergo chemotherapy due to patient refusal and 4 patients because of early discontinuation of chemotherapy with poor general condition. Two patients had poor quality of CT images after chemotherapy.

Treatment policy and clinical follow-up. Chemotherapy regimens consisted of carboplatin+paclitaxel (n=3), carboplatin+docetaxel (n=7), cisplatin+docetaxel (n=2), carboplatin+gemcitabine (n=3), cisplatin+gemcitabine (n=3), carboplatin+etoposide (n=1). One patient had a concurrent chemoradiotherapy. After treatment each patient was monitored regularly. During the follow-up, complete physical examination, chest CT, routine laboratory test were performed every 6 months.

F-18 FDG PET/CT. F-18 FDG PET/CT images were required before and 3 cycle after chemotherapy. 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. 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.

Tumor response. CT tumor response was determined using Response Evaluation Criteria in Solid Tumors (RECIST), which considers a 30% or greater reduction in the sum of uni-dimensional tumor measurement as a response [12]. Metabolic response was evaluated based on visual analysis in all patients.

For quantitative analysis, changes of SUV_{max} ($\% \Delta SUV_{max}$) after chemotherapy was obtained in all patients. Because most of patients of the current study had multiple lesions at F-18 FDG PET/CT, the most hypermetabolic lesion was taken as an index lesion and from these lesions, the $\% \Delta SUV_{max}$ was calculated. PET response was defined as the presence of a significant decrease in the metabolism of the index lesion by direct comparison of the pre- and postchemotherapy scans as determined by a reading nuclear physician or the resolution of hypermetabolic area in part or all of the known malignant lesions.

Statistical analysis. All numerical data were expressed as mean \pm SD. Survival analysis was conducted using Kaplan-Meier analysis, and survival curves stratified by F-18 FDG PET response and CT response were generated. Log rank test was used to compare the survival between responder and non-responder of each of F-18 FDG PET and CT images. Overall survival was measured from the date of first diagnosis to the date of death or most recent follow-up. 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 $P < 0.05$.

Results

Patient characteristics and follow-up. The characteristics of the patients are given in Table 1. Fifteen patients were male (78.9%) The mean age at the time of diagnosis was 64.2 \pm 8.1 years. Ten patients had adenocarcinoma and 9 patients had squamous cell carcinoma. The median follow-up time was overall 24.8 month (range, 9.4~59.8 month), for surviving patients 41 month (range, 34.1~59.8 month), and for deceased

Table 1. Patients characteristics.

Characteristics	All patients N=19 (%)
Sex	
Male	15 (78.9%)
Female	4 (21.1%)
Age at diagnosis	
Median	65
Range	51~81
Tumor histologic type	
Squamous cell carcinoma	9 (47.3%)
Adenocarcinoma	10 (52.7%)
Treatment	
Chemotherapy	18 (94.7%)
Chemotherapy+Radiotherapy	1 (5.3%)
Clinical stage	
IIIa	7 (36.8%)
IIIb	5 (26.4%)
IV	7 (36.8%)

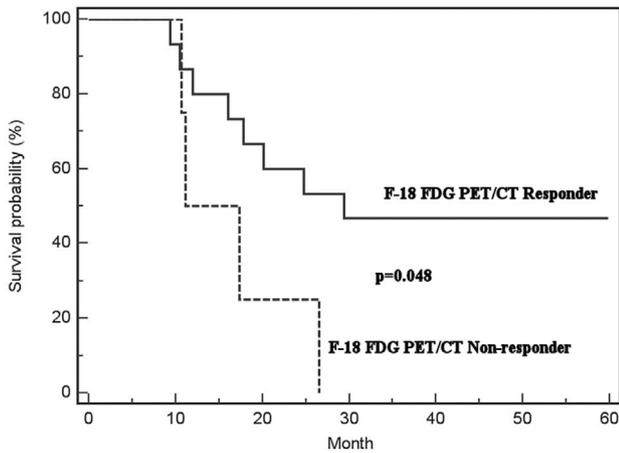


Figure 1. Kaplan-Meier curve of survival stratified by visual assessment of F-18 FDG PET/CT tumor response.

patients 16.6 month (range, 9.4~29.4 month). Overall survival after baseline F-18 FDG PET/CT at 1 year was 73.7% and at 2 year was 47.4%.

Prognostification by visual F-18 FDG PET/CT tumor response. On visual analysis of F-18 FDG PET/CT, 15 patients (78.9%) responded to treatment and 4 patients did not respond. Comparing patients with and without F-18 FDG PET/CT response, there was statistically significant difference in overall survival between the 2 groups (median survival time, responder, 29.4 month; non-responder, 14.2 month, $X^2=3.91$, $p=0.048$, Figure 1).

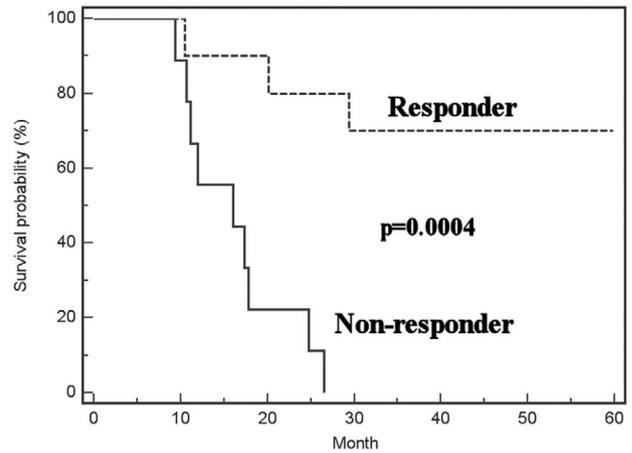


Figure 2. Kaplan-Meier curve of survival stratified by $\% \Delta SUV_{max}$.

Prognostification by $\% \Delta SUV_{max}$. Using the $\% \Delta SUV_{max}$ for the comparison of survival between responder and non-responder, there was statistically significant difference in overall survival between 2 groups ($X^2=12.6$, $p=0.0004$, Figure 2).

Prediction of survival by quantitative indices. Figure 3 demonstrates the comparison of $\% \Delta SUV_{max}$ between F-18 FDG PET/CT responder and non-responder. The overall median $\% \Delta SUV_{max}$ after treatment was a -17.85% (range, -98.2%~66.9%). For those of responder, mean $\% \Delta SUV_{max}$ was a -25.9% (range, -98.2%~30.7%) and for non-responder, mean $\% \Delta SUV_{max}$ was a 26.2% (range, -11.2%~66.9%). ROC analysis

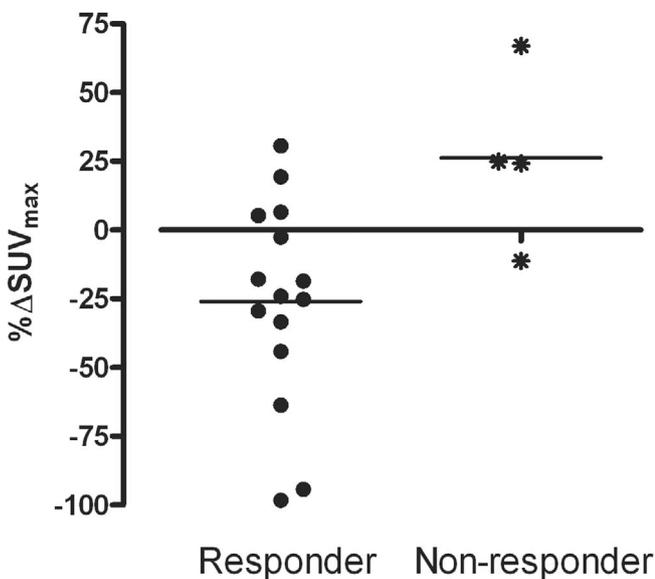


Figure 3. Comparison of $\% \Delta SUV_{max}$ between responder and non-responder after chemotherapy in patients with advanced stage NSCLC.

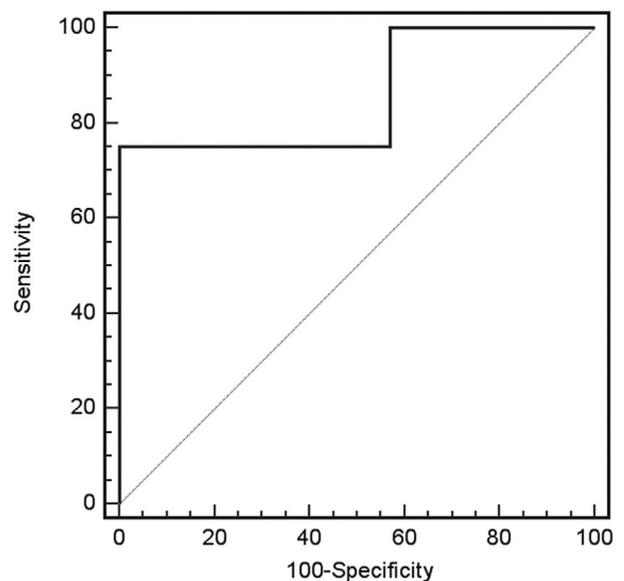


Figure 4. ROC analysis for predicting survival after chemotherapy using quantitative index of F-18 FDG PET/CT.

Table 2. Analysis of prognostic factors for survival

Variables	Hazard ratio	95% confidence interval	P value
Age	0.51	0.13~2.72	0.5055
Sex	0.57	0.18~3.21	0.6216
Histology	0.92	0.42~2.43	0.29
Clinical stage	1.14	0.55~1.83	0.2026
% Δ SUV _{max}	2.81	1.12~6.75	0.017
Visual PET response	0.88	0.33~1.78	0.3801

was performed for the prediction of survival after treatment by % Δ SUV_{max}. When the tumor reveals more than 17.85% reduction of % Δ SUV_{max}, the survival could be predicted in the current study (Figure 4, AUC, 0.857; standard error, 0.0866; 95% confidence interval, 0.622~0.971; sensitivity, 75%; specificity, 100%; $p=0.0001$).

Prognostic factors. In order to define the prognostic factors, multivariate survival analysis was performed using Cox proportional hazard model. Table 2 shows that only the % Δ SUV_{max} was determined to be a potent prognostic factor for survival (X^2 , 12.09; $p=0.0005$), but the other variables were not significant factors in multivariate survival analysis.

Discussion

The current study shows that % Δ SUV_{max} of tumor as measured by F-18 FDG PET/CT possesses a potent prognostic value in patients with advanced stage (stage III and IV) NSCLC. Also, when the tumor reveals more than 17.85% reduction of % Δ SUV_{max}, the survival could be predicted in the current study. On visual analysis of F-18 FDG PET/CT, responder had a longer overall survival than non-responder (median survival time, responder, 29.4 month; non-responder, 14.2 month).

Tumor response after chemotherapy is a crucial factor of cancer patient's survival. Traditionally, morphologic tumor responses using CT, magnetic resonance imaging, and others have been used. However, these tumor response evaluations based on anatomical changes before and after treatment had several weak points. F-18 FDG PET/CT has emerged as a significant molecular imaging technique in clinical oncology and cancer research [13–15]. Tumor response evaluation by F-18 FDG PET and PET/CT appears to be more sensitive and accurate because F-18 FDG PET is able to assess viable tumor cells.

A number of studies suggested that F-18 FDG PET had a prognostic value in NSCLC patients [16–20]. Most of these studies evaluated SUV in primary tumor before and after treatment and they founded that FDG uptake in primary tumor could predict overall survival with different thresholds of SUV. However, few data are available on the effect of changes of such quantitative indices on survival of treated NSCLC. A recent

study reported that patients with a decrease in SUV_{max} of > 50% in primary tumor had a higher overall 2-year survival rate as compared with patients with a decrease of SUV_{max} < 50% [21]. Another study concluded that a greater than 60% decrease of SUV_{max} was indicative for a favorable 5 year survival, whereas a less than 25% decrease could indicate unfavorable prognosis [22]. Another recent study also found that the 5-year overall survival rate for patients with cleared or persistent minor mediastinal lymph node involvement was significantly higher in patients with a more than 60% decrease in SUV_{max} on the primary tumor as compared with patients with a less than 60% decrease in SUV_{max} (62% v 13%; log-rank $p=0.002$) (8). Cerfolio et al [23] found that when the SUV_{max} decreased by 80% or more, a complete pathologic response could be predicted with a sensitivity of 90%, specificity of 100%, and accuracy of 96%. Their report showed that the percentage of change in the SUV_{max} on FDG-PET scan after neoadjuvant treatment was an accurate predictor of the actual pathologic response of the primary tumor and that it also can identify complete responders. However, using serial measurement of SUV_{max} in 47 patients with stage III NSCLC, significant differences in SUV_{max} were observed either before ($p_1=0.003$) or after ($p_2=0.002$) treatment between the responder and non-responder groups. However, the percent change of SUV_{max} before and after therapy were not significantly different ($p=0.054$) (9).

In the current study, we tried to define the optimal value of % Δ SUVmax in predicting the prognosis of advanced staged NSCLC patients. ROC analyses revealed that when the tumor reveals more than 17.85% reduction of % Δ SUV_{max}, the survival could be predicted in the current study with optimal sensitivity and specificity. Compared to other researches, the current study had a relative low threshold value of % Δ SUV_{max} for prediction of prognosis. Because the current study included limited number of patients and each patient had a wide range of % Δ SUV_{max} after 3 cycles of chemotherapy. To obtain optimal value of % Δ SUV_{max} for the prediction of survival of NSCLC, homogenous large number population-based future study is needed.

Whether the % Δ SUVmax could be used for the prediction survival in patients with advanced stage NSCLC is controversial and remains to be debatable. A number of previous studies focused on the implication of quantitative indices of SUV_{max} and SUV_{mean} for the prediction of recurrent and/or metastatic diseases instead of predicting survival. Therefore, few data is available for this problematic issue until now.

Recent studies mainly investigated the relationships of the changes of SUV after treatment and pathologic response in various tumors including NSCLC [6, 24–26]. However, these studies also investigated the primary tumor SUV values effect on prognosis and whether the changes of SUV values after treatment could predict pathologic response to treatment.

In the current study, both of the visual assessment of tumor response and % Δ SUV_{max} of F-18 FDG PET/CT could predict survival of advanced stage NSCLC patients. Also, responder to chemotherapy had a better prognosis than non-responder

group. However, with Cox proportional hazard model, the $\% \Delta \text{SUV}_{\text{max}}$ was the only potent predictor of survival in advanced stage NSCLC.

In conclusion, using the visual and quantitative analyses of F-18 FDG PET/CT, the responder to chemotherapy in advanced stage NSCLC patients had a better prognosis. Moreover, the potent predictor of prognosis in advanced stage NSCLC patients was $\% \Delta \text{SUV}_{\text{max}}$.

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