# Correlation between $^{18}$F-Fluorodeoxyglucose Uptake and Epidermal Growth Factor Receptor Mutations in Advanced Lung Cancer

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# Correlation between $^{18}$F-Fluorodeoxyglucose Uptake and Epidermal Growth Factor Receptor Mutations in Advanced Lung Cancer

Directed by Professor Jong Doo Lee

The Master's Thesis
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of
Master of Medical Science

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June 2012

This certifies that the Master's Thesis of
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June 2012

# ACKNOWLEDGEMENTS

First of all, I would like to show my gratitude to Professor Jong Doo Lee, who is my thesis director. His encouragement, guidance and support in every step of the process enabled me to develop an understanding of the subject.

Also, I am indebted to Professor Won Jun Kang and ByoungChul Cho, for their help on pertinent advice to assure superior quality of this paper.

I owe my deepest gratitude to Professor Mijin Yun and Tae JooJeon, for helpful suggestions that gave inspiration to this paper.

In addition, I want to show an appreciation to my parents, and all family members who always support me.

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ABSTRACT

# Correlation between $^{18}$F-Fluorodeoxyglucose Uptake and Epidermal Growth Factor Receptor Mutations in Advanced Lung Cancer

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**Purpose:** Mutations in the epidermal growth factor receptor (EGFR) gene have been identified as potential targets for treatment of and prognostic factors for non-small cell lung cancer (NSCLC). We assessed the correlation between fluorodeoxyglucose (FDG) uptake and EGFR mutations, as well as their prognostic implications.
**Methods:** A total 163 patients with pathologically confirmed NSCLC were enrolled (99 males and 64 females; median age, 60 years). All patients underwent FDG positron emission tomography before treatment, and genetic studies of EGFR mutations were performed. The maximum standardized uptake value ($SUV_{MAX}$) of the primary lung cancer was measured and normalized with regard to liver uptake. The $SUV_{MAX}$ between the wild-type and EGFR mutant groups was compared. Survival was evaluated according to $SUV_{MAX}$ and EGFR mutation status.
**Results:** EGFR mutations were found in 57 patients (60.8%).The $SUV_{MAX}$ tended to be higher in wild-type than mutant tumors but was not significantly different (11.1 ± 5.7 vs. 9.8 ± 4.4, $P$ = 0.103). The $SUV_{MAX}$ was significantly lower in patients with an exon 19 mutation than those with either an exon 21 mutation or wild-type ($P$ =

0.003 and 0.009, respectively). The EGFR mutation showed prolonged overall survival (OS) compared to wild-type tumors (P = 0.004). There was no significant difference in survival according to$SUV_{MAX}$. Both OS and progression-free survival of patients with a mutation in exon 19 were significantly longer than in patients with wild-type tumors.

**Conclusion:** In patients with NSCLC, mutation in exon 19 associated with a lower $SUV_{MAX}$ is a reliable predictor for good survival, and is a potential target of EGFR therapy.

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Key words : Non-small cell lung cancer,$^{18}$F-fluoro-2-deoxy-D-glucose positron emission tomography ($^{18}$F-FDG PET), epidermal growth factor receptor (EGFR) gene

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## I. INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide[1-3] and is pathologically and clinically categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is the major form of lung cancer and is classified into several histologic types: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma[4]. At the time of initial diagnosis, two-thirds of patients with NSCLC are inoperable status, including locally advanced or metastatic tumors, and many patients who undergo curative surgery suffer from the recurrence of this cancer[5]. Despite improvements in diagnostic and therapeutic approaches, the clinical outcome of patients with lung cancer is still poor[1].

With recent advances in molecular research, molecularly targeted agents such as gefitinib, an epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), have emerged as promising treatment in advanced NSCLC[6,7]. The EGFR pathway is regarded to be a key signal transduction pathway in cancer cell proliferation and tumor invasion[7]. Mutations in the EGFR gene have been identified as potential therapeutic targets for the treatment of patients with NSCLC[8]. However, genetic

analyses require invasive tissue biopsies. Some studies have attempted to identify imaging characteristics of EGFR mutations by computed tomography(CT), but decisive findings have not been described[9].

$^{18}$F-Fluoro-2-deoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) has been demonstrated to be very useful in the diagnosis and staging of NSCLC[10]. The rate of $^{18}$F-FDG uptake in the primary site of NSCLC has been associated with tumor doubling time, proliferation rates, and overall survival (OS) after surgical resection[10-12]. In addition,$^{18}$F-FDG uptake is positively correlated with tumor status, node status, and metastasis status, and is an independent predictor of prognosis[13].

Several studies have investigated the relationship between EGFR mutation and $^{18}$F-FDG uptake. However, they have revealed opposite results. Na et al. suggested that low $^{18}$F-FDG uptake predicts the presence of EGFR mutations in patients with NSCLC[14]. On the other hand, Huang et al. suggested that higher $^{18}$F-FDG uptake is more likely to result from an EGFR mutation among Asian patients with advanced lung adenocarcinoma[15]. The purpose of this study is to investigate the relationship between EGFR mutation status and $^{18}$F-FDG uptake in advanced NSCLC. In addition, we assessed the prognostic implications of FDG uptake and EGFR mutation status.

## II. MATERIALS AND METHODS

### *1. Patients*

We retrospectively reviewed 1,052 patients who underwent $^{18}$F-FDG PET/CT for lung cancer staging between 2004 and 2010 at a single institution. We excluded the following patients: (1) patients with a histologic type of SCLC, (2) patients with pathologic stage I/II, and (3) patients whose tissue samples were unavailable for genetic analyses. A total of 163 patients were selected for the final analysis. Pathologic tumor staging was performed using the revised International Association for the Study of Lung Cancer[16].

***2. Imaging Procedure***

All patients fasted for at least 4 hours and had a serum glucose level less than 140 mg/dL before the IV injection of $^{18}$F-FDG. Scanning was initiated 60 minutes after $^{18}$F-FDG administration. Images from the neck to the proximal thighs were obtained using either a GE PET scanner (GE Advance, GE Healthcare) with a spatial resolution of 5 mm in the center of the field of view or a Philips PET system (Allegro, Philips-ADAC Medical Systems) with a spatial resolution of 5.3 mm in the center of the field of view. For the GE Advance scanner, approximately 370 MBq$^{18}$F-FDG was injected intravenously, and PET image acquisition was performed at 5-minute intervals per bed position in two-dimensional mode. The Allegro scanner acquired data in a three-dimensional mode after the intravenous administration of 5.18 MBq/kg $^{18}$F-FDG. Transmission scans (3-minute intervals per bed position) using $^{68}$Ge for the GE Advance scanner or $^{137}$Cs for the Allegro scanner were obtained for non-uniform attenuation correction, and interleaved between the multiple emission scans for the Allegro scanner. The obtained images were reconstructed using an iterative reconstruction algorithm, specifically, using either the ordered-subset expectation maximization for the GE Advance scanner or the row-action maximal likelihood algorithm for the Allegro scanner. For semi-quantitative analysis, a region of interest was placed over the area of maximum activity in the primary lung cancer. The maximum standard uptake value ($SUV_{MAX}$) corrected for total body weight was calculated within the region of interest. The $SUV_{MAX}$ of the liver was used to control for any differences in technique between the scans. The normalized $SUV_{MAX}$ was calculated as the ratio of the $SUV_{MAX}$ of the primary tumor to the $SUV_{MAX}$ of the liver.

***3. EGFR Mutation Analysis***

Genomic DNA was extracted from the tumor specimen, and EGFR tyrosine kinase exons 18–21 were amplified by nested polymerase chain reaction using specific primers. The details of the sequencing procedure are described elsewhere[17,18]. The presence of EGFR mutations was determined by mutations in exon 19 and exon 21.

### *4. Statistical Analysis*

Continuous variables were analyzed using the Student's *t* test, and the results were expressed as the mean ± standard deviation. The Pearson's chi-square test was used to analyze the categorical variables. Multivariate logistic regression analysis was performed to test the association between clinical factors and EGFR mutations. Both progression-free survival (PFS) and OS were calculated from the initiation of targeted therapy (gefitinib). Kaplan-Meier estimates of PFS and OS were calculated in the patients who received TKI treatment. A P-value less than 0.05 was considered statistically significant. All analyses were performed using SPSS software (Version 18.0; SPSS Incorporation, Chicago, IL).

## III. RESULTS

### *1. Patients Characteristics*

Table 1 shows the characteristics of the patients. Ninety-nine patients (60.8%) were males, and the median age was 60 years (range: 30–84 years). Seventy-nine percent of the patients had adenocarcinomas, and 55.2 percent of patients never smoked. The $SUV_{MAX}$of primary tumors ranged from 2.14 to 30.5 (median: 10.7). EGFR mutations were found in 57 patients (35%): an exon 19 deletion was found in 30 patients, and an L858R substitution in exon 21 was found in 27 patients.

**Table 1** Patient characteristics

| Characteristics | Number of patients (%) |
|---|---|
| Age (years) | |
| <64 | 100 (61.3) |
| ≥64 | 63 (38.7) |
| Gender | |
| Female | 64 (39.2) |
| Male | 99 (60.8) |
| Smoking status | |
| Never smoked | 90 (55.2) |
| Current or former smoker | 73 (44.8) |
| IASLC disease status | |
| III | 67 (41.1) |
| IV | 96 (58.9) |
| Histology | |
| Adenocarcinoma | 130 (79.7) |
| Squamous | 27 (16.6) |
| Others | 6 (3.7) |
| Total | 163 |

*IASCL* International Association for the Study of Lung Cancer

2. ***Relationship Between Clinical Features And EGFR Mutation***

Associations between clinical features and EGFR mutations were evaluated using univariateand multivariate analyses. Results are listed in Table 2. EGFR mutations were more frequent in patients who never smoked than in those who smoked (23.3% versus 11.7%; P = 0.031), in patients with adenocarcinoma than in patients without adenocarcinoma (33% versus 1.8%; P < 0.0001), and in females than in males (20% versus 14%; P < 0.0001). By multivariate analysis, smoking history was the only factor that was significantly associated with EGFR mutation (p < 0.0001).

**Table2** Relationship between clinical features and EGFR mutation

| Characteristics | Number of patients with EGFR mutation (%) | Univariate*P* value | Multivariate *P* value RR (95% CI) |
|---|---|---|---|
| Age (years) | | 0.744 | 0.796 |
| <64 | 34 (20.8) | | |
| ≥64 | 23 (14.1) | | |
| Gender | | <0.0001 | 0.061 |
| Female | 33 (20.2) | | |
| Male | 24 (14.8) | | |
| Smoking status | | 0.031 | <0.0001 |
| Never smoked | 38 (23.3) | | −0.007(−0.01−0.003) |
| Current of former smoker | 19 (11.7) | | |
| IASLC disease status | | 0.633 | 0.951 |
| III | 22 (13.5) | | |
| IV | 35 (21.5) | | |
| Histology | | <0.0001 | 0.051 |
| Adenocarcinoma | 54 (33.1) | | |
| Others | 3 (1.8) | | |
| Total | 57 | | |

*RR* relative risk, *CI* confidence interval, *IASCL* International Association for the Study of Lung Cancer

### *3. Assiciation Between EGFR Mutation And $SUV_{MAX}$ Of PrimaryTumors*

The mean $SUV_{MAX}$ of wild-type NSCLC was 11.1 ± 5.7 and that of EGFR mutant NSCLC was 9.8 ± 4.4 (Fig. 1). The $SUV_{MAX}$of wild-type NSCLC tended to be higher than that of mutant NSCLC, but was not significantly different ($P$ = 0.103). In contrast, the mean $SUV_{MAX}$ of wild-type adenocarcinoma was 11.0 ± 5.2 and that of EGFR mutant adenocarcinoma was 9.3 ± 4.0, and there was a statistically significant difference ($P$ = 0.044; Fig. 2). The mean $SUV_{MAX}$ of the L858R mutant was 11.6 ± 4.9 and that of the in-frame deletion mutant was 8.2 ± 3.3 (Fig. 3). The $SUV_{MAX}$ was

significantly lower in the in-frame deletion in exon 19 mutant than in either the L858R mutant ($P$ = 0.003) or wild-type NSCLC ($P$ = 0.009). There was no significant difference in the $SUV_{MAX}$ between the L858R mutant and wild-type NSCLC ($P$ = 0.87; Fig. 3).

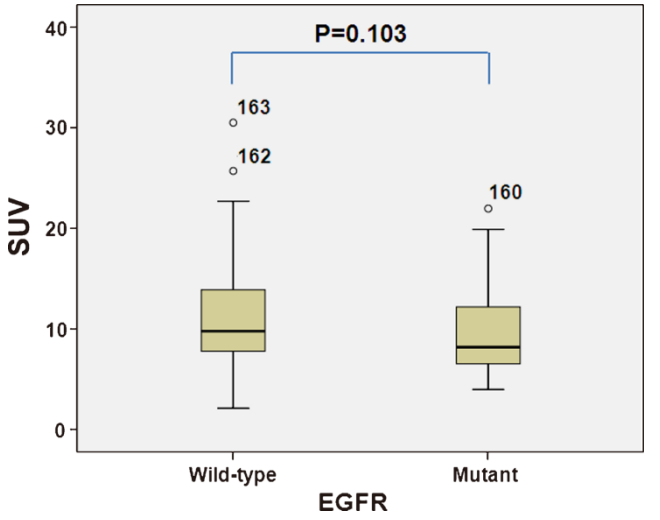


**Fig. 1** Box plot of $SUV_{MAX}$ for patients with wild-type and mutant EGFR NSCLC

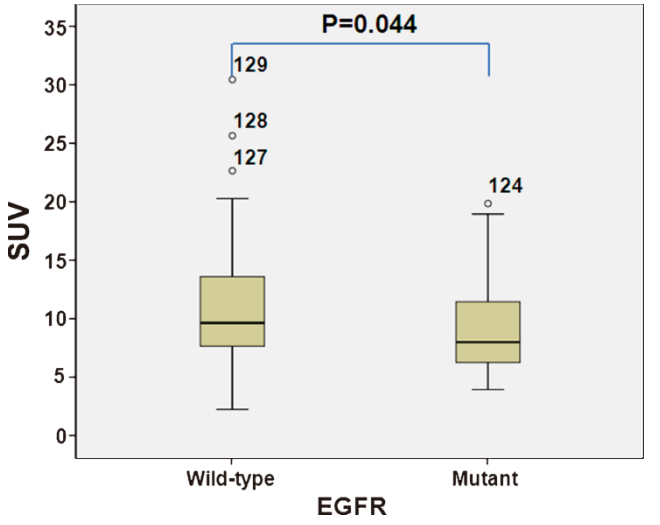


**Fig. 2** Box plot of $SUV_{MAX}$ for patients with wild-type and mutant EGFR

adenocarcinoma

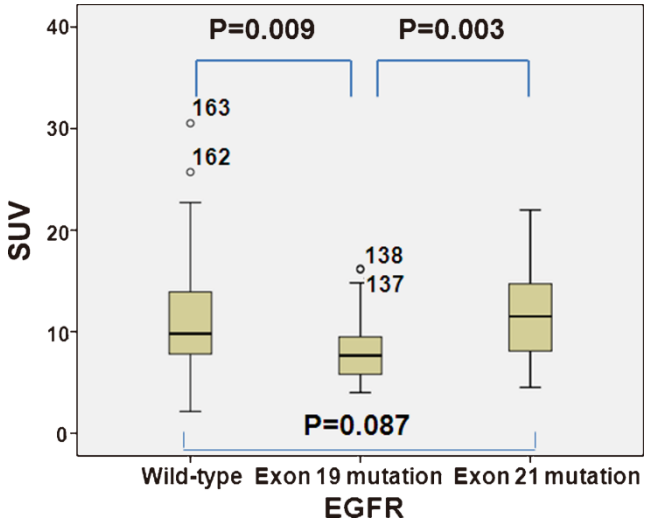


**Fig. 3** Box plot of $SUV_{MAX}$ for patients with an in-frame deletion of exon 19 and an L858R substitution in exon 21

### *4. Association Between EGFR Mutation And Normalized $SUV_{MAX}$*

The mean normalized $SUV_{MAX}$ of the wild-type NSCLC was 11.1 ± 5.7 and that of the in-frame deletion in exon 19 mutant was 3.6 ± 1.9. The mean normalized $SUV_{MAX}$ of the L858R mutant was 5.3 ± 2.53 (Fig. 4). The normalized $SUV_{MAX}$ was significantly lower in the in-frame deletion mutant than in either the L858R mutant ($P$ = 0.004) or wild-type NSCLC ($P$<0.001). There was no significant difference in the normalized $SUV_{MAX}$ between the L858R mutant and wild-type NSCLC ($P$ = 0.77).

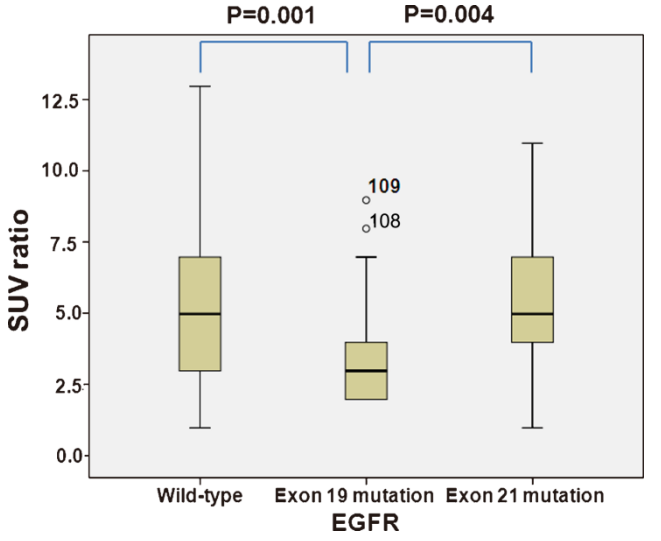


**Fig. 4** Box plot of normalized $SUV_{MAX}$ for patients with wild-type, an in-frame deletion of exon 19, and an L858R substitution in exon 21 tumors

### *5. $SUV_{MAX}$ And Survival*

Eighty-three patients received gefitinib treatment, and 36 patients had an EGFR mutation. The median OS of all patients was 819 days (95% CI, 544.3–1093.3 days). Patients with EGFR mutations had longer OS than those without EGFR mutations (P = 0.004). According to the $SUV_{MAX}$ values ($SUV_{MAX}$< 10 vs. $SUV_{MAX} \geq 10$), survival differences did not reach statistical significance (P = 0.354). When PFS was analyzed, the median PFS was 202 days (95% CI, 160.8 $SUV_{MAX}$ 243.5 days). EGFR mutation and $SUV_{MAX}$ ($SUV_{MAX}$ < 10 vs. $SUV_{MAX} \geq 10$) did not confer statistically different outcomes in terms of PFS (P = 0.066 and 0.086, respectively; Fig. 5).

According to EGFR mutation type, the OS and PFS of patients with the in-frame deletion were significant longer than patients with wild-type tumors (P = 0.042 and 0.021, respectively). However, there were no significant differences in OS and PFS between patients with either the L858R mutation or wild-type tumors (P = 0.285 and 0.638, respectively; Fig. 6).

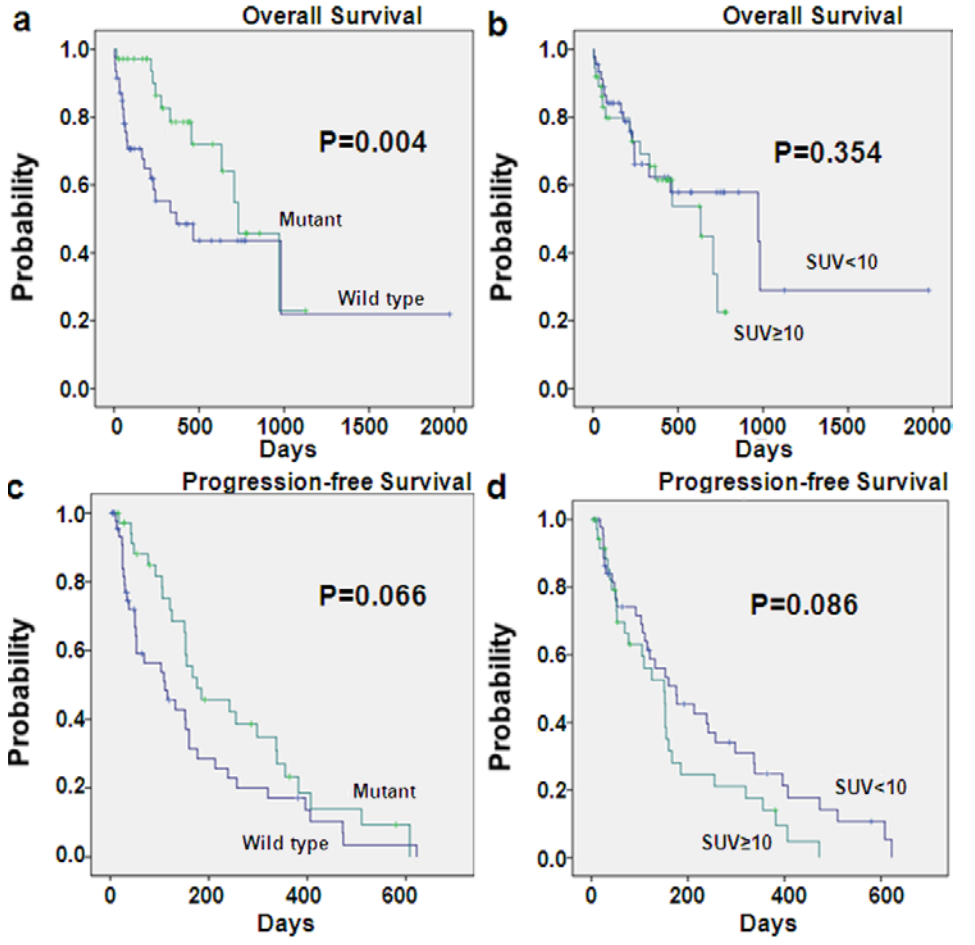


**Fig. 5** (**a)** Kaplan-Meier plots of overall survival (OS) according to EGFR mutation. (**b**) Kaplan-Meier plots of OS according to SUV. (c) Kaplan-Meier plots of progression-free survival according to EGFR mutation. (d) Kaplan-Meier plots of OS according to SUV

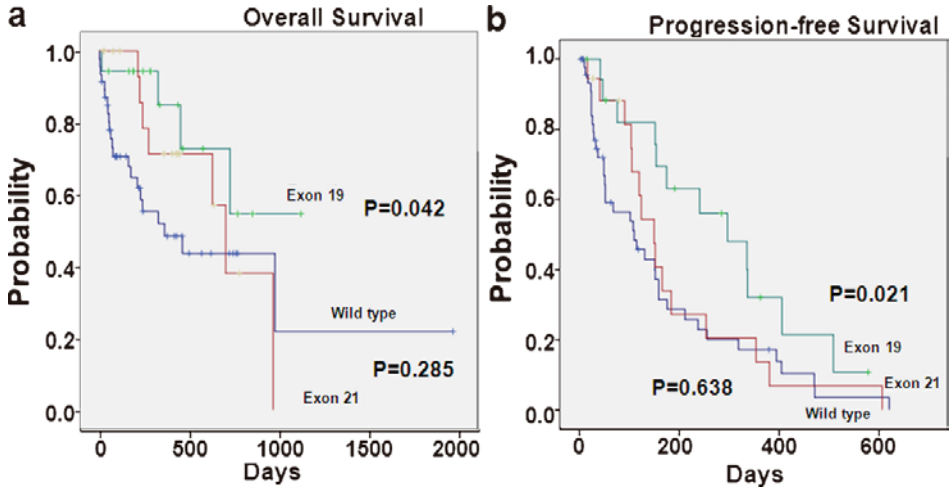


**Fig. 6** (**a**) Kaplan-Meier plots of overall survival according to EGFR mutation type. (**b**) Kaplan-Meier plots of progression-free survival according to EGFR mutation type

## IV. DISCUSSION

In the present study, we demonstrated that $^{18}$F-FDG uptake of wild-type NSCLC tended to be higher than that of EGFR-mutant NSCLC. Specifically, we found that patients with an exon 19 mutation showed low FDG uptake and favorable survival.

To our knowledge, only a few studies have evaluated the association between $^{18}$F-FDG uptake and EGFR mutation. However, these studies suggested conflicting results[14,15,19]. In a Taiwanese study of 77 patients with adenocarcinoma including 49 mutant EGFR and 28 wild-type EGFR tumors, $^{18}$F-FDG uptake was significantly higher in mutant EGFR tumors (mean $SUV_{MAX}$, 10.5 ± 4.7) than in wild-type EGFR tumors (mean $SUV_{MAX}$, 8.0 ± 3.3)[15]. In contrast, a Korean study of 100 NSCLC patients, including 21 patients with EGFR mutant tumors, demonstrated that a low SUV might be associated with the presence of an EGFR mutation[18]. Furthermore, a recent study of a predominantly white population with NSCLC, including 24 patients with EGFR mutant tumors, showed that high $^{18}$F-FDG avidity correlated with wild-type NSCLC[19]. Our results support those of the latter two studies, demonstrating that low SUV correlates with EGFR mutation. In addition, we showed that the exon 19

mutation is strongly correlated with low $SUV_{MAX}$, and subsequent favorable survival. However, previous studies did not perform analyses according to the mutant type.

Our study differed from previous studies in several points. We enrolled exclusively stage III and IV patients, because EGFR-TKI is mainly considered in advanced tumor stages. Furthermore, restriction of patients to those with advanced tumor stages has an advantage in survival analysis. Another important difference was that we analyzed the data according to mutation types. In addition, previous studies did not show survival analysis and correlation between $SUV_{MAX}$ and EGFR mutation status.

Our results are consistent with those from previous studies such that EGFR mutations are found predominantly in female patients, in patients with adenocarcinoma histology, and in those who have never smoked[14,20]. We conducted molecular analyses to detect the in-frame deletion in exon 19 and L858R in exon 21. Some studies demonstrated that different classes of EGFR mutations might vary clinically and pathologically in terms of their downstream signaling pathways and responsiveness to EGFR TKI[21,22]. Previous studies suggested that the in-frame deletion and L858R mutations are important to determine TKI sensitivity[23-25]. Furthermore, the in-frame deletion might be predictive of longer PFS following EGFR TKI treatment[26]. In our study, patients with the in-frame deletion showed significantly lower $^{18}$F-FDG uptake and longer OS and PFS. More studies analyzing the differences in FDG uptake according to mutant types are needed.

Although EGFR mutation is a useful tool to predict TKI responsiveness, tissues from patients with advanced cancer stages are frequently insufficient to perform genetic tests. In such cases, non-invasive methods to estimate the probability of EGFR mutation status would be helpful. Our findings suggest that low FDG avidity in the primary tumor is associated with a high possibility of an in-frame deletion in exon 19, which is a good predictor of the success of EGFR TKI treatment.

One study showed that SUVs may vary depending on the method used[27], and another that factors that can alter SUVs are body size, amount of injected tracer, blood volume, and body mass index[28]. In our study, we calculated the ratio of the $SUV_{MAX}$ in the primary tumor to the $SUV_{MAX}$ in the liver for standardization. However, the results were similar in the $SUV_{MAX}$ of primary tumors and thus normalized $SUV_{MAX}$. Therefore, the $SUV_{MAX}$ of primary tumors can be used conveniently.

This study has the following limitations. First, it was performed in a retrospective manner, and selection bias cannot therefore be avoided. Second, although we enrolled more subjects than in previous studies, our enrollment of 163 is still too small for a detailed analysis. More large-scale studies are needed.

## V. CONCLUSION

In conclusion, lower $^{18}$F-FDG uptake of primary tumors was associated with an in-frame deletion of exon 19 in patients with NSCLC. Although genetic tests are the gold standard, $^{18}$F-FDG uptake may provide useful information when this j test is not feasible.

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ABSTRACT (IN KOREAN)

# 진행성폐암에서상피성장인자수용체유전자돌연변이의유무에따른양전자방출단층촬영술에서의섭취정도와예후와의관계

<지도교수이종두>

연세대학교대학원의학과

최윤정

**연구목적**: 진행성 비소세포폐암에서 상피성장인자수용체의 유전자 돌연변이는 표적치료를 결정하는 인자이며, 예후예측인자로 알려져 있다. 이 논문에서는 양전자방출단층촬영술에서의 섭취 정도와 상피성장인자수용체의 유전자 돌연변이, 예후와의 관계를 규명하고자 하였다.

**대상및방법**: 2004년 1월부터 2010년 12월까지 신촌세브란스병원에서 비소세포폐암을 진단받고, 치료 전 병기결정을 위해 양전자방출단층촬영술을 시행한 163명의 환자를 대상으로 상피성장인자수용체의 유전자 돌연변이의 종류와 원발병소의 $SUV_{MAX}$를 비교하였으며, 상피성장인자수용체의 유전자 돌연변이의 종류와 $SUV_{MAX}$에 따른 생존율과 무재발생존율을 분석하였다.

**결과:** 상피성장인자수용체의 유전자 돌연변이는 60.8% (57/163)의 환자에서 발견되었으며, 전체 비소세포폐암에서 상피성장인자수용체의 유전자 돌연변이가 있는 군과 돌연변이가 없는 군은 $SUV_{MAX}$에 통계학적으로 유의한 차이가 없었다(11.1±5.7 vs. 9.8±4.4, $P$=0.103). 하지만 Exon 19에 돌연변이가 있는 군은 Exon 21에 돌연변이가 있는 군이나, 돌연변이가 없는 군에 비해 $SUV_{MAX}$가 통계학적으로 유의하게 낮은 것을 관찰할 수 있었다

(*P*=0.003 and 0.009). 상피성장인자수용체의 유전자 돌연변이가 있는 군은 돌연변이가 없는 군에 비해 생존기간이 짧았으나, $SUV_{MAX}$에 따른 생존율이나 무재발생존율에는 통계학적으로 유의한 차이가 없었다. Exon 19에 돌연변이가 있는 군은 Exon 21에 돌연변이가 있는 군이나 돌연변이가 없는 군에 비해 생존율과 무재발생존율이 높은 것을 관찰할 수 있었다.
결론: 비소세포폐암에서 상피성장인자수용체의 유전자 Exon 19에 돌연변이가 있는 군은 낮은 $SUV_{MAX}$를 보이며, 좋은 예후를 나타낸다.

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핵심되는말: 비소세포폐암, 상피성장인자수용체의유전자돌연변이, 양전자방출단층촬영술