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

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Abstract

Purpose Mutations in the epidermal growth factor receptor (EGFR) gene have been identified as potential targets for the treatment 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 of 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 (SUVmax) of the primary lung cancer was measured and normalized with regard to liver uptake. The SUVmax between the wild-type and EGFR mutant groups was compared. Survival was evaluated according to SUVmax and EGFR mutation status.

Results EGFR mutations were found in 57 patients (60.8 %). The SUVmax 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 SUVmax was significantly lower in patients with an exon 19 mutation than in 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 SUVmax. Both OS and progression-free survival of patients with a mutation in exon 19 were significant longer than in patients with wild-type tumors.

Conclusion In patients with NSCLC, a mutation in exon 19 was associated with a lower SUVmax and is a reliable predictor for good survival.

Keywords 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

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 histological types: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [4]. At the time of initial diagnosis, two-thirds of patients with NSCLC have inoperable disease, including locally advanced or metastatic tumors, and many patients who undergo curative surgery suffer from recurrent NSCLC [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

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emerged as promising treatments 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, 11]. 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, 13]. In addition, ^{18}F -FDG uptake is positively correlated with tumor status, node status, and metastasis status, and is an independent predictor of stage [14, 15].

Several studies have investigated the relationship between EGFR mutation and ^{18}F -FDG uptake. However, they have revealed opposite results. Na et al. [16] suggested that low ^{18}F -FDG uptake predicts the presence of EGFR mutations in patients with NSCLC. However, Huang et al. [17] suggested that higher ^{18}F -FDG uptake is more likely to result from an EGFR mutation among Asian patients with advanced lung adenocarcinoma. 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.

Materials and Methods

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 histological type of SCLC, (2) patients with pathological 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. Pathological tumor staging was performed using the revised International Association for the Study of Lung Cancer [18].

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 had never smoked. The SUVmax 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

IASLC International Association for the Study of Lung Cancer

Imaging Procedure

All patients fasted for at least 4 h and had a serum glucose level less than 140 mg/dl before the IV injection of ^{18}F -FDG. Scanning was initiated 60 min 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-min 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-min 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 (SUVmax) corrected for total

body weight was calculated within the region of interest. The SUVmax of the liver was used to control for any differences in technique between the scans. The normalized SUVmax was calculated as the ratio of the SUVmax of the primary tumor to the SUVmax of the liver.

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 [19, 20]. The presence of EGFR mutations was determined by mutations in in-frame deletion within exon 19 and L858R point mutation in exon 21.

Statistical Analysis

Continuous variables were analyzed using Student's *t*-test, and the results were expressed as the mean $\pm$ standard deviation. 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).

Results

Relationship between Clinical Features and EGFR Mutations

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

Association between EGFR Mutation and SUVmax of Primary Tumors

The mean SUVmax of wild-type NSCLC was 11.1 ± 5.7 and that of EGFR mutant NSCLC was 9.8 ± 4.4 (Fig. 1). The

Table 2 Relationship between clinical features and EGFR mutation

Characteristics	Number of patients with EGFR mutation (%)	Univariate <i>P</i> value	Multivariate <i>P</i> 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 or 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, IASLC International Association for the Study of Lung Cancer

SUVmax 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 SUVmax 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 SUVmax of the L858R mutation in exon 21 was 11.6 ± 4.9 and that of the in-

Fig. 1 Box plot of SUVmax for patients with wild-type and mutant EGFR NSCLC

frame deletion in exon 19 was 8.2 ± 3.3 (Fig. 3). The SUVmax was significantly lower in the in-frame deletion in the 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 SUVmax between the L858R mutant and wild-type NSCLC ($P=0.87$) (Fig. 3).

Association between EGFR Mutation and Normalized SUVmax

The mean normalized SUVmax 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 SUVmax of the L858R mutant was 5.3 ± 2.53 (Fig. 4). The normalized SUVmax was significantly lower in the in-frame deletion in exon 19 than in either the L858R mutation in exon 21 ($P=0.004$) or wild-type NSCLC ($P<0.001$). There was no significant difference in the normalized SUVmax between the L858R mutant and wild-type NSCLC ($P=0.77$)

SUVmax 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 SUVmax values (SUVmax <10 vs. SUVmax ≥ 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 SUVmax 243.5 days). EGFR mutation and SUVmax (SUVmax <10 vs. SUVmax ≥ 10) did not confer statistically different outcomes in terms of PFS ($P=0.066$ and 0.086, respectively) (Fig. 5).

Fig. 2 Box plot of SUVmax for patients with wild-type and mutant EGFR adenocarcinoma

Fig. 3 Box plot of SUVmax for patients with an in-frame deletion of exon 19 and an L858R substitution in exon 21

According to EGFR mutation type, the OS and PFS of patients with the in-frame deletion in exon 19 were significantly longer than in 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 in exon 21 or wild-type tumors ($P=0.285$ and 0.638, respectively) (Fig. 6).

Discussion

In the present study, 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

Fig. 4 Box plot of normalized SUVmax for patients with wild type, an in-frame deletion of exon 19, and an L858R substitution in exon 21 tumors

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

association between ^{18}F -FDG uptake and EGFR mutation. However, these studies suggested conflicting results [16, 17, 21]. 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 SUVmax, 10.5 ± 4.7) than in wild-type EGFR tumors (mean SUVmax, 8.0 ± 3.3) [17]. 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 [20]. 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 [21]. Our results support those of

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

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 [16, 22]. 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 [23, 24]. Previous studies suggested that the in-frame deletion in exon 19 and L858R mutations in exon 21 are important to determine TKI sensitivity [25–27]. Furthermore, the in-frame deletion in exon 19 might be predictive of longer PFS following EGFR TKI treatment [28]. In our study, patients with the in-frame deletion in exon 19 showed significantly lower ¹⁸F-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 [29], and another that factors that can alter SUVs are body size, amount of injected tracer, blood volume, and body mass index [30]. 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, this study 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.

Conclusion

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

Conflicts of interest The authors declare that they have no conflict of interest.

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