Prognostic Value of SUVmax Measurements Obtained by FDG-PET in Patients with Non-Small Cell Lung Cancer Receiving Chemotherapy

Yohei Imamura,[1] Koichi Azuma[1], Seiji Kurata[2], Satoshi Hattori[3], Tetsuro Sasada[4],Takashi Kinoshita[1], Masaki Okamoto[1], Tomotaka Kawayama[1],Kaida Hayato[2], Masatoshi Ishibashi[2] and Hisamichi Aizawa[1]

Authors' Affiliations: [1]Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, [2]Department of Radiology, Kurume University School of Medicine, Kurume, Japan; [3]Biostatistics Center, Kurume University, Kurume, Japan; [4]Cancer Vaccine Center, Dana-Farber Cancer Institute, Boston, MA 02115, USA

Requests for reprints: *Koichi Azuma, Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan. Tel.: +81-942-31-7560; Fax: +81-942-31-7703; E-mail: azuma@med.kurume-u.ac.jp*

Running title: FDG-PET predicts PFS and OS in NSCLC patients receiving chemotherapy

Abbreviations: NSCLC, non-small cell lung cancer; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; SUV, standardized uptake value; SUVmax, maximum standardized uptake value; PCR, polymerase chain reaction; OS, overall survival; PFS, progression-free survival; CT, computed tomography; CR, complete response; PR, partial response; PD, progressive disease: SD, stable disease; ROI, region of interest; CI,

confidence interval; HR, hazard ratio; TLG, total lesion glycolysis

ABSTRACT

[^{18}F]Fluorodeoxyglucose (FDG) uptake has been shown to correlate well with tumor proliferation rates. In patients with non-small cell lung cancer (NSCLC) receiving chemotherapy, we analyzed the relationships between the maximum standardized uptake value (SUVmax) obtained by FDG positron emission tomography (FDG-PET) and other clinical factors, and examined whether or not SUVmax could predict progression-free survival (PFS) and/or overall survival (OS). This retrospective study involved 62 consecutive NSCLC patients (35 male and 27 female: median age, 65 years). All patients underwent FDG-PET examination before treatment. As the first-line treatment, the patients received chemotherapy with (n = 15) or without (n = 47) radiotherapy. Survival curves were obtained by the Kaplan-Meier method, and differences in survival between subgroups were analyzed by the log-rank test and the Cox proportional hazards model. Significant correlations were observed between SUVmax and gender (P = 0.006), histology (P < 0.001), smoking status (P = 0.049), stage (P = 0.015), and treatment modality (P = 0.008), but not other factors, including age (P = 0.402) and performance status (P = 0.421). The median SUVmax was 5.1 (25^{th} – 75^{th} percentile: 3.45-7.0) in patients with adenocarcinoma and 8.3 (25^{th} – 75^{th} percentile: 6.9-9.9) in those with other types of NSCLC. Adenocarcinomas showed significantly lower SUVmax than the other tumor types (P < 0.001). Cox analysis adjusting for possible confounding factors, including gender, smoking status, histology and stage, demonstrated that the hazard ratios increased as the SUVmax increased in terms of both PFS (P = 0.008) and OS (P = 0.045), indicating that SUVmax predicts outcome independently of other clinical factors, such as histology and stage. Our findings indicate

that FDG-PET examination can provide information useful for prognostication in NSCLC.

Introduction

Lung cancer continues to be the leading cause of cancer death worldwide. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 80% of all cases, and includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The treatment of lung cancers is dependent on histological subtype and disease stage. More than half of all patients have metastasis at the time of diagnosis, and chemotherapy is the most effective treatment for those with advanced disease (1-2).

In recent years, the clinical use of [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) has emerged as a non-invasive diagnostic tool and become widespread. PET is a quantitative imaging technique that measures external radiation from a positron-emitting radiopharmaceutical in tissues as function of time and space. This imaging modality exploits the fact that most malignancies metabolize glucose at a much higher rate than normal tissues. The uptake of FDG correlates with tumor cell proliferation, and has been suggested to be an independent prognostic factor in patients with various types of cancer. In clinical examinations of NSCLC patients, FDG-PET has been reported to be useful for the characterization of pulmonary nodules, the staging of mediastinal lymph nodes, and the detection of distant metastases (3-6). Previous studies have suggested that the standardized uptake value (SUV), which has been used to quantitatively evaluate FDG uptake on FDG-PET, is associated with the outcome of patients with NSCLC (7-9). In addition, recent studies have demonstrated that low SUV is associated with favorable outcome in patients with advanced NSCLC, who have been treated with gefitinib or

platinum-based chemotherapy (9-10).

Several biological markers that have value for predicting the response to chemotherapeutic agents have been identified in NSCLC. For example, the absence or presence of mutations within the kinase domain of the epidermal growth factor receptor (EGFR) gene in lung adenocarcinoma cells has a key role in determining the therapeutic efficacy of the EGFR-targeting drugs, gefitinib and erlotinib, whose development has been a recent milestone in this field. Indeed, about 80% of tumors possessing EGFR mutations respond to EFGR/tyrosine kinase-targeting drugs (11, 12). Excision repair cross-complementation group 1 (ERCC1) is a component of the nucleotide excision repair pathway, which is essential for the repair of platinum–DNA adducts, and is associated with cellular resistance to platinum compounds (13, 14). Thioredoxin, p53, BRCA, and ribonucleotide reductase subunit M1 (RRM1) are also associated with platinum-drug resistance (13-15). The drawback of these markers, however, is that tumor tissues need to be obtained by biopsy or resection for immunohistochemistry or polymerase chain reaction (PCR) analysis, and diagnostic certainty may sometimes be compromised by tissue sampling error and/or tissue heterogeneity. In contrast, FDG-PET is a non-invasive diagnostic tool that can provide intrinsic biological information about tumors, and is expected to have great prognostic value for indicating the malignant potential of various tumor types. In the present study, we retrospectively analyzed the relationships between maximum SUV (SUVmax) and other clinical factors, and examined whether or not SUVmax could predict progression-free survival (PFS) and/or overall survival (OS) of NSCLC patients receiving chemotherapy.

Materials and Methods

Patients and treatment

This retrospective study involved 62 consecutive NSCLC patients treated at a single institution (Kurume University Hospital, Kurume, Japan). All patients received chemotherapy between April 2004 and March 2008. Details of the patients' clinical characteristics, including age, gender, histology, smoking status, performance status, stage, and treatment modality, were obtained from chart review by an independent reviewer unaware of the results of SUVmax measurements (Table 1). Of these patients, 35 were male, and 27 were female with a median age of 65 (range 35-82) years. The tumor histology was classified as adenocarcinoma in 39 patients, squamous cell carcinoma in 12, adenosquamous cell carcinoma in 2, large cell carcinoma in 5, and unclassified in 4, on the basis of the World Health Organization (WHO) criteria. According to the Tumor-Node-Metastasis (TNM) classification of malignant tumors, 1 patient had stage IIB, 13 had stage IIIA, 7 had stage IIIB, and 41 had stage IV. All the patients received chemotherapy with (n = 15) or without (n = 47) radiotherapy as the first-line treatment for NSCLC. Tumor responses were evaluated after chemotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST) (16). All patients underwent chest X-ray examinations and computed tomography (CT) scans of the chest and upper abdomen, bone scans, and brain magnetic resonance imaging (MRI) before chemotherapy, and at least every 6 weeks during chemotherapy. Complete response (CR) was defined as the disappearance of all clinically detectable tumor lesions, lasting for at least 4 weeks. Partial response (PR) was defined as a decrease of at least 30% in the sum of the longest dimensions of the target

lesions for at least 4 weeks, with no appearance of new lesions. Progressive disease (PD) indicated an increase of at least 20% in the sum of the longest dimensions of the target lesions or the emergence of new lesions. Stable disease (SD) was defined as a decrease in tumor lesions that was insufficient to qualify as PR and an increase that was insufficient to qualify as PD.

PET image analysis

PET scans were obtained using a dedicated PET scanner (Allegro; Philips Medical Systems, Cleveland, OH, USA). All patients were fasted, except for water, for more than 4 hours before the PET scan. All of them had normal blood glucose levels (range; 80-120 mg/dl) when measured immediately before the scan. Just before injection of ^{18}F-FDG, they were hydrated with 500 ml of water. Image acquisitions for the whole body scan started approximately 60 min after intravenous administration of 7.00 $\pm$ 1.44 mCi of ^{18}F-FDG. The patients then underwent scanning from the base of the skull to the midthighs with transmission attenuation correction (2 minutes and 30 seconds/bed position emission, 23 seconds/bed position transmission). Attenuation-corrected emission images were reconstructed using the three-dimensional row action maximum likelihood algorithm (3D-RAMLA; Philips, Eindhoven, Netherlands) (17). After image reconstruction, a region of interest (ROI) was carefully drawn around each lesion site. This analysis was performed uniformly by an experienced nuclear medicine physician for the entire population examined. From the ROI, the SUV was calculated according to the formula: (ROI activity [mCi/mL])/(injected dose [mCi]/body weight [g]). The SUVmax of ^{18}F-FDG was measured

from the ROI, which was placed at the site of the lesions on the PET scans.

Statistical methods

Wilcoxon's rank-sum test was applied to compare the SUVmax distribution of adenocarcinoma patients with that of others. Patients were classified into two groups using a cut-off SUVmax of 6.0, close to the median SUVmax of 6.6 (range:1.7-18.1): low (<6) and high (>6) SUVmax groups. Overall response rates (CR or PR) and disease control rates (CR, PR, or SD) were calculated. Relationships between SUVmax and various characteristics or tumor responses to treatment were compared between the low and high SUVmax groups using Fisher's exact test. OS was defined as the number of days from the start of chemotherapy until death due to any cause. PFS was defined as the number of days from the start of chemotherapy until disease progression or death due to any cause. For these two time-to-event endpoints, the following statistical analysis was conducted. Survival functions of the low and high SUVmax groups were estimated by the Kaplan-Meier method, and compared using the log-rank test. The Cox proportional hazards model with adjustment for possible confounding factors was applied to evaluate the influence of SUVmax. Factors that were shown to be significantly associated with SUVmax by Fisher's exact test or with PFS and/or OS by the log-rank test were regarded as possible confounding factors. In the Cox regression, SUVmax was treated as a continuous variable instead of a categorized variable (the low and the high SUVmax groups) to avoid loss of information due to categorization. All tests were two-sided, and a P value <0.05 was considered to indicate statistical significance. All statistical analyses were conducted using JMP version 8, SAS version 9.1

software (SAS Institute Inc., Cary, NC) and R version 2.9.0.

Results

Relationships between SUVmax and various clinical characteristics

Table 2 shows the relationships between measured SUVmax and various clinical characteristics, including, age, gender, histology, smoking status, performance status, stage, and treatent modality. The high SUVmax group included 35 patients, and the low SUVmax group included 27 patients. A significant correlation was observed between SUVmax measurements and gender ($P = 0.006$), histology ($P < 0.001$), smoking status ($P = 0.049$), stage ($P = 0.015$), and treatment modality ($P = 0.008$), but not other factors, including age ($P = 0.402$) and performance status ($P = 0.421$). This finding indicated that lower SUVmax was associated with female gender, adenocarcinoma, never having smoked, advanced stage (IIIB and IV), and chemotherapy. Fig. 1 shows the relationship between measured SUVmax and tumor histological type. The median SUVmax was 5.1 (25^{th} – 75^{th} percentile: 3.45-7.0) in patients with adenocarcinoma and 8.3 (25^{th} – 75^{th} percentile: 6.9-9.9) in those with other types of NSCLC; adenocarcinomas showed significantly lower SUVmax than the other types of cancer ($P < 0.001$).

Tumor reponse to treatment

The chemotherapy regimens employed were platinum doublet in 48 patients (carboplatin–paclitaxel, 18; cisplatin–vinorelbine, 16; cisplatin–tegafur/uracil (UFT), 5; carboplatin–gemcitabine, 3; cisplatin–docetaxel, 4; cisplatin–irrinotecan, 1; cisplatin-etoposide, 1), platinum triplet (cisplatin–vinorelbine-gemcitabine) in 7,

non-platinum doublet (gemcitabine-vinorelbine) in one, monotherapy in 2 (gemcitabine, 1; docetacel, 1), and EGFR tyrosine kinase inhibitor (gefitinib) in 4. Among them, 15 patients received radiotherapy in combination with chemotherapy (cisplatin–vinorelbine, 6 patients; cisplatin–tegafur/uracil (UFT), 5; cisplatin–docetacel, 2; cisplatin-etoposide, 1; carboplatin-paclitaxel, 1). The median number of chemotherapy cycles was three (range 1 to 4). The relationships between SUVmax and tumor responses to treatment are shown in Table 3. The overall response rate (CR or PR) in the low SUVmax group was 29.6% (2 CR and 6 PR), whereas that in the high SUVmax group was 62.9% (1 CR and 21 PR); the overall response rate differed significantly between the low and high SUVmax groups (P = 0.012). On the other hand, the disease control rate (CR, PR or SD) was 88.9% and 77.1% in the low and high SUVmax group, respectively; the disease control rates in the two groups were comparable, and not significantly different (P = 0.321).

Associations between SUVmax and progression-free or overall survival

The median follow-up time was 464 (range 81 to 1621) days, and the median progression-free and overall survival times were 227 (range 22 to 1200) and 464 (range 81 to 1621) days, respectively. As shown in Figs 2A and 2B, Kaplan-Meier estimates for all 62 patients demonstrated that those in the low SUVmax group had longer OS (P = 0.017, Fig 2B), but not longer PFS (P = 0.609, Fig 2A), than those in the high SUVmax group. To reduce the heterogeneity of treatments between patients, Kaplan-Meier estimates were calculated for a subgroup of 47 patients who received chemotherapy only, and are also shown in Figs. 2C and 2D. In this subgroup, patients in the low SUVmax group had longer

PFS (P = 0.013, Fig. 2C) and OS (P = 0.024, Fig 2D) than those in the high SUVmax group. These results suggest that the lack of statistical significance for SUVmax by the log-rank test for PFS in all 62 patients may have been due to the influence of confounding factors. Therefore, the hazard ratio (HR) for the high SUVmax group relative to the low group was estimated using the Cox proportional hazards model in all 62 patients, by adjusting for possible confounding factors, including gender, smoking status (never-smoker and smoker), stage (IIB-IIIA and IIIB-IV) and histology (adnocarcinoma and others). For this analysis, stage, but not treatment modality, was adjusted for, since treatment modality (chemotherapy or chemoradiotherapy) was often dependent on, and highly correlated with, disease stage. Table 5 shows the results of the Cox regression analysis. The HR for the unit change of SUVmax was estimated to be 1.14 (95% CI: 1.04, 1.25, P = 0.008) for PFS and 1.12 (95% CI: 1.00, 1.25, P = 0.045) for OS, indicating that patients with higher SUVmax had a worse outcome than those with lower SUVmax after adjustment for other clinical factors, such as histology and stage.

Discussion

Previous studies have demonstrated that lower SUV uptake on FDG-PET is associated with better prognosis in patients with NSCLC (5-7). In addition, it has recently been shown that lower SUV uptake is correlated with favorable outcomes in patients with advanced NSCLC receiving gefitinib or platinum-based chemotherapy (9-10). Although the data are variable, patients with primary tumors that show a high metabolic rate tend to exhibit a more aggressive clinical course than those whose tumors show a low metabolic rate. In agreement with these results, the present study demonstrated that SUVmax had a significant impact on progression-free ($P = 0.008$) and overall ($P = 0.045$) survival in NSCLC patients who received chemotherapy in the Cox regression analysis. Surprisingly, however, disease stage had a statistical significance only on progression-free survival ($P = 0.004$), but not on overall ($P = 0.629$) survival. These findings indicate that SUVmax measurements may be useful for prognostication of NSCLC patients.

In the present study, we examined the relationship between measured SUVmax and treatment response rate (CR or PR). Interestingly, among the 62 patients who received chemotherapy or chemoradiotherapy, the response rate in the low SUVmax group was 29.6%, whereas that in the high group was 62.9%. Patients with a high SUVmax associated with a poor outcome showed a significantly higher response rate than those with a low SUVmax. On the other hand, the disease control rate in the high SUVmax group was comparable to, or slightly lower, than that in the low SUVmax group. In general, shrinkage of tumors detected by CT after chemotherapy reflects a reduction of tumor load and is believed to translate into a survival benefit (18). For example, previous studies of patients

with advanced or metastatic NSCLC have shown that response to chemotherapy as determined by CT scan after 8weeks of treatment is a predictor of subsequent survival (19). However, although tumor shrinkage seems to be a necessary precondition for improved survival in some cancer patients, clinical studies involving a variety of chemotherapeutic agents have not consistently demonstrated a correlation between the response to treatment and patient survival. Indeed, some clinical trials suggest that patients with lung cancer derive a clinical benefit from treatment that helps stabilize their disease (20). Concomitant with these studies, our present data suggested that there was no significant difference in survival between patients with PR and those with SD, although patients with PR or SD had longer survival than those with PD.

We could not conclude which regimens are more effective for NSCLC patients with a high SUVmax, because the regimens were heterogenous and varied between individual patients in this study. However, since most of the patients (chemotherapy group 42/48 = 88%, chemoradiotherapy group 15/15 = 100%) received platinum-based regimens, we speculate that patients with a high SUVmax associated with a poor outcome may have a significantly higher response rate to platinum compounds than those with a low SUVmax in patients with NSCLC. Analysis of the molecular factors predicting the chemosensitivity and prognosis of patients treated with chemotherapies has been considered important for understanding the tumor biology of NSCLC and deciding on better therapeutic strategies. Treatment with inadequate chemotherapy regimens may cause various undesirable side effects without benefits, whereas administration of effective drugs selected according to their predicted effects could help improve survival and/or quality of life. Therefore, it will

be really important to examine which regimens are more effective for NSCLC patients with a high SUVmax in future studies

In this study, we further examined whether SUVmax could also be correlated with other factors in NSCLC, which might affect prognosis. Significant correlations were observed between SUVmax and gender ($P = 0.006$), histology ($P < 0.001$), smoking status ($P = 0.049$), stage ($P = 0.015$), and treatment modality ($P = 0.008$), but not other factors, including age ($P = 0.402$) and performance status ($P = 0.421$). Previously, Vesselle et al. reported that bronchioalveolar carcinoma had lower FDG uptake and lower Ki-67 scores than other histologic types, and that non-bronchioalveolar adenocarcinoma had lower FDG uptake and lower Ki-67 scores than squamous cell carcinoma or large-cell undifferentiated carcinoma (21). Moreover, Casali et al also reported that the SUVmax values were significantly related to histological subtypes (22). Coincident with these reports, we found that adenocarcinomas showed significantly lower SUVmax than the other NSCLC types ($P < 0.001$). This may be associated with difference in the SUVmax between males and females, because females show a higher frequency of adenocarcinoma than other types of cancers. The differences of SUVmax may be explainable by derangement of glucose metabolism in NSCLC. In a previous study of lung cancers, for example, the FDG uptake of tumors was reportedly correlated with the level of expression of glucose transporter (GLUT)-1 and hexokinase (23). GLUT-1 was expressed in 100% of squamous cell carcinomas, but in only 58% of adenocarcinomas (24). The different expression patterns of these molecules may reflect the levels of FDG uptake in tumors with different histology. Further studies are needed to clarify the relationship between molecular characteristics and

FDG uptake in tumors.

In the current study, we measured SUVmax in tumors. Recently, however, a different method of evaluating tumor metabolism, such as total lesion glycolysis (TLG), has been available. Unlike SUVmax, which is a measurement of metabolic activity per body weight and reflects only the point of greatest metabolic activity within tumors, TLG has been suggested to better reflect tumor metabolic activity by taking into account the activity in the entire tumor. In fact, TLG has been reported to be a promising indicator of metabolic activity in several different malignancies, such as breast cancer and osteosarcoma (25, 26). Although original methods of measuring TLG, which required the manual drawing of numerous consecutive regions of interest throughout the entire tumor, were labor-intensive, a manufacturer-provided software for TLG measurement has been developed. It will be interesting to compare the SUVmax with a different measurement, such as TLG, in predicting survival in NSCLC patients in future studies.

Currently, paraffin-embedded specimens obtained by bronchial biopsy are the usual materials available for molecular characterization of tumors by PCR or immunohistochemical analysis to predict the survival of patients with advanced NSCLC. However, such samples are sometimes too small to allow detection of molecular signatures in heterogeneous cancer tissues. The present findings suggest that FDG-PET, which has been employed extensively as a non-invasive and valuable imaging tool for diagnosis and staging in NSCLC, may be beneficial for predicting the survival of NSCLC patients, although there were some limitations in this study, such as the use of retrospective analysis for a limited number of patients. As a further step, a larger-scale prospective randomized

control study employing homogeneous standard regimens will be recommended to verify the roles of FDG-PET. To achieve wider clinical use of FDG-PET for prognostication, the methodology for determining the appropriate threshold of SUVmax needs to be optimized and standardized. Prospective multi-institutional trials employing standardized imaging protocols will also be required to determine the significance of FDG-PET for prognostication of cancer patients.

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Conflict of interest statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Figure legends

Fig. 1. Relationship between measured SUVmax and tumor histology. SUVmax measurements were compared between adenocarcinomas and other types of tumors. Adenocarcinomas showed significantly lower SUVmax than the other types of NSCLC ($P < 0.001$).

Fig. 2. Kaplan-Meier survival analysis of NSCLC patients with low (<6) and high (>6) SUVmax measurements.

A, B: Kaplan-Meier estimates for PFS (A) and OS (B) in all 62 patients, who received chemotherapy or chemoradiotherapy. The patients with high SUVmax had shorter OS ($P = 0.017$), but not shorter PFS ($P = 0.609$), than those with low SUVmax. Differences between subgroups were analyzed by the log-rank test.

C, D: Kaplan-Meier estimates for PFS (C) and OS (D) in a subgroup of 47 patients who received chemotherapy only. The patients with high SUVmax had shorter PFS ($P = 0.013$) and OS ($P = 0.024$) than those with low SUVmax. Differences between subgroups were analyzed by the log-rank test.

Fig.1

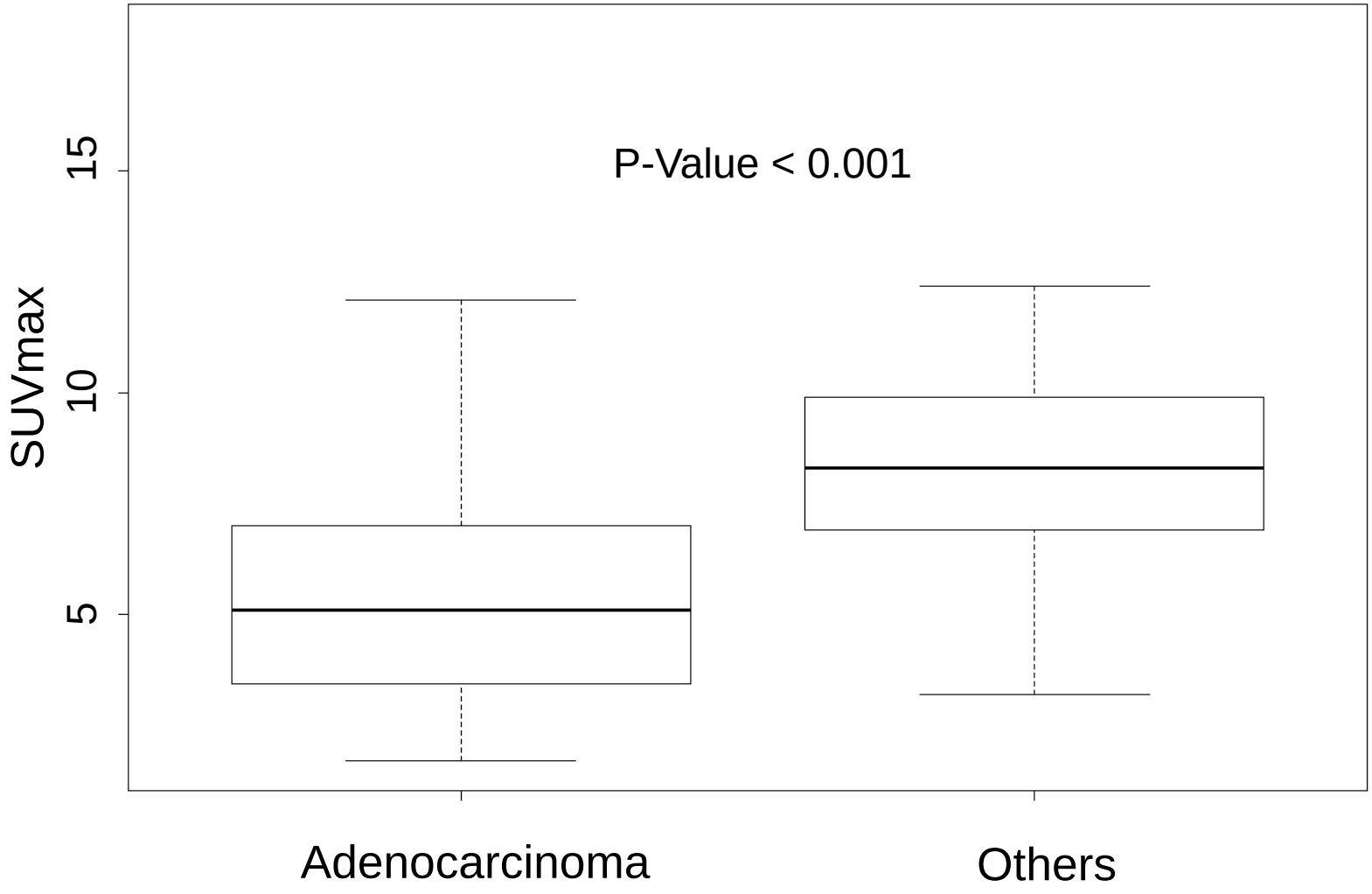

Fig.2

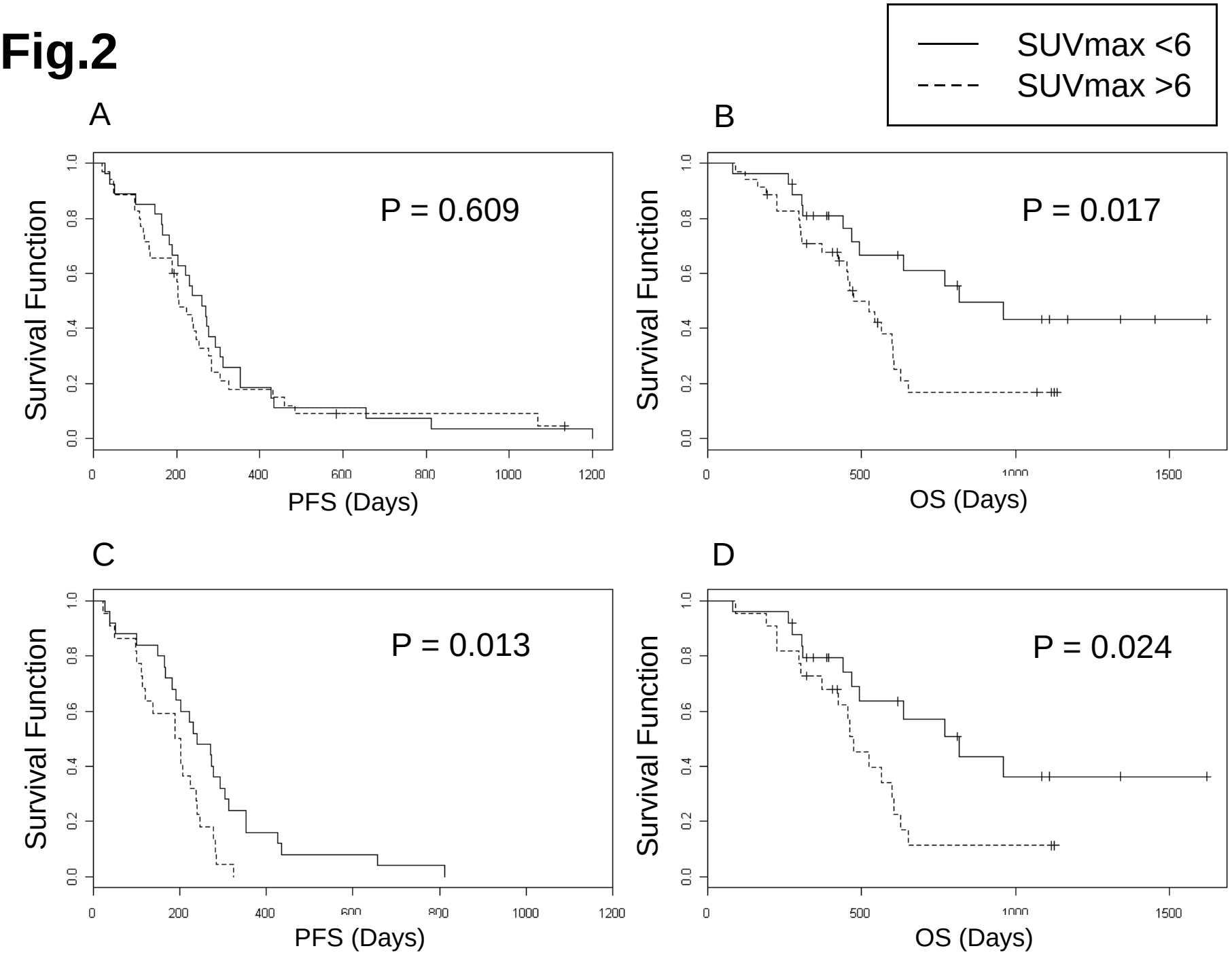
SUVmax <6
SUVmax >6
A
P = 0.609
Survival Function
PFS (Days)
B
P = 0.017
Survival Function
OS (Days)
C
P = 0.013
Survival Function
PFS (Days)
D
P = 0.024
Survival Function
OS (Days)

Table 1: Patients' characteristics

Characteristics		Number
Age (years)		
	Median	65
	Range	35-82
Gender		
	Male	35
	Female	27
Histology		
	Adenocarcinoma	39
	Squamous cell carcinoma	12
	Adenosquamous cell carcinoma	2
	Large cell carcinoma	5
	Unclassified	4
Smoking status		
	Never smoker	28
	＜50 pack-year	17
	≧50 pack-year	17
Perfomance status		
	0	50
	1	12
Stage		
	IIB	1
	IIIA	13
	IIIB	7
	IV	41
Treatment modality		
	Chemotherapy	47
	Chemoradiotherapy	15

Table 2: Relationship between SUVmax and various characteristics

Characteristics	Number	High SUVmax (6>)	Low SUVmax (<6)	P-value*
Age (years)				
High (≧65)	33	17	16	P = 0.402
Low (＜65)	29	18	11	
Gender				
Male	35	25	10	P = 0.006
Female	27	10	17	
Histology				
Adenocarcinoma	39	14	25	P < 0.001
Others	23	21	2	
Smoking status				
Never-smoker	28	12	16	P = 0.049
Smoker	34	23	11	
Performance status				
0	50	27	23	P = 0.421
1	12	8	4	
Stage				
IIB-IIIA	14	12	2	P = 0.015
IIIB-IV	48	23	25	
Treatment modality				
Chemotherapy	47	22	25	P = 0.008
Chemoradiotherapy	15	13	2	

* By Fisher's exact test

Table 3: Relationship between SUVmax and tumor response to treatment

Tumor response†	Low SUVmax (<6)	High SUVmax (>6)	P-value*
CR	2	1	
PR	6	21	
SD	16	5	
PD	3	8	
Overall response rate (CR or PR)	8/27 = 29.6%	22/35 = 62.9%	P = 0.012
Disease control rate (CR, PR, or SD)	24/27 = 88.9%	27/35 = 77.1%	P = 0.321

*By Fisher's exact test, †CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Table 4: Summary of univariate analysis for progression-free and overall survival

Factor	Number	Progression-free survival		Overall survival	
		Median (days)	Univariate analysis (Log-rank)	Median (days)	Univariate analysis (Log-rank)
Age (years)					
High (≧65)	29	253	P = 0.220	600	P = 0.700
Low (＜65)	33	203		565	
Gender					
Male	35	230	P = 0.916	565	P = 0.439
Female	27	239		606	
Smoking status					
Never-smoker	28	255	P = 0.883	636	P = 0.269
Smoker	34	206		544	
Performance status					
0	50	230	P = 1.000	565	P = 0.794
1	12	221		600	
Histology					
Adenocarcinoma	39	246	P = 0.830	771	P = 0.002
Others	23	224		451	
Treatment modality					
Chemotherapy	47	206	P = 0.001	565	P = 0.507
Chemoradiotherapy	15	431		603	
Stage					
IIB-IIIA	14	325	P = 0.017	603	P = 0.976
IIIB-IV	48	223		565	
SUVmax					
6>	27	262	P = 0.609	817	P = 0.017
6<	35	206		474	

Table 5: Influence of SUVmax on progression-free survival and overall survival after adjusting for possible confounding factors.

Factor		Progression-free survival		Overall survival	
		Hazard ratio (95% CI*)	P-value	Hazard ratio (95% CI*)	P-value
SUVmax	linear	1.14 (1.04, 1.25)	P = 0.008	1.12 (1.00, 1.25)	P = 0.045
Gender	Female/Male	1.62 (0.37, 7.13)	P = 0.521	4.60 (0.30, 70.36)	P = 0.272
Smoking status	Smoker/Never-smoker	1.39 (0.32, 6.13)	P = 0.660	3.00 (0.20, 44.77)	P = 0.425
Histology	Others/Adenocarcinoma	0.85 (0.42, 1.71)	P = 0.640	2.48 (1.03, 5.95)	P = 0.042
Stage	IIIB-IV/IIB-IIIA	2.88 (1.42, 5.87)	P = 0.004	1.23 (0.53, 2.84)	P = 0.629

*CI, confidence interval