Influence of Thyroid Transcription Factor-1 on Fluorodeoxyglucose Uptake and Prognosis of Non-small Cell Lung Cancer

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Abstract. *Aim: To assess the correlation between thyroid transcription factor-1 (TTF1) protein expression in primary tumors from patients with non-small cell lung cancer (NSCLC) and fluorodeoxyglucose (FDG) uptake, and to determine its effect on survival outcomes. Patients and Methods: We categorized 112 patients with NSCLC according to TTF1 expression ($TTF1^+$: n=59, $TTF1^-$: n=53), and retrospectively determined whether positron-emission topography measurements, including standardized uptake values [mean (SUV_m) and maximum (SUV_{max})], metabolic tumor volume (MTV), total lesion glycolysis (TLG), and other clinical factors could predict progression-free (PFS) or overall (OS) survival of these patients. Results: The SUV_m, SUV_{max}, MTV, and TLG values were lower in the $TTF1^+$ group; their survival outcomes were also better. The SUV_m, SUV_{max}, and TLG values were good prognostic indicators for OS and PFS in this group. Conclusion: Primary NSCLC tumors expressing TTF1 had lower FDG uptake than those that did not and this was a good prognostic indicator.*

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Lung cancer is the leading cause of cancer-related death worldwide but despite therapeutic advances, the prognosis of patients with lung cancer has only minimally improved (1). Positron-emission tomography (PET) uptake of fluorodeoxyglucose (FDG) in tumors is proportional to the metabolic rate of viable tumor cells and might, therefore, help predict the biological aggressiveness of a tumor. Studies have shown that the degree of tumor uptake of FDG during PET, which is reflected by the mean standardized uptake value (SUV_m), maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), is useful for predicting the overall (OS) and progression-free (PFS) survival of patients with lung cancer.

Thyroid transcription factor 1 (TTF1) is a master regulatory transcription factor for tissue-specific genes (2) and its overexpression was associated with a favorable prognosis in patients with NSCLC in a recent meta-analysis (3).

However, FDG uptake and TTF1 expression have been reported separately as prognostic indicators (3, 4) and the effect of TTF1 expression by NSCLC tumors on FDG uptake remains unknown. We, therefore, assessed the correlation between TTF1 expression and FDG uptake to determine the effect on survival outcomes.

Patients and Methods

Patient population. We retrospectively reviewed the medical records of all patients with histopathologically-confirmed NSCLC who had undergone FDG-PET/computed tomography (CT) before receiving any therapy at our cancer Center between January 2007 and December 2012. The study was approved by the Human Research Ethics Committee of our institution (Buddhist Tzu Chi General Hospital, Dalin. B10201023).

Table I. *Patients' clinicopathological characteristics.*

Characteristic	
Gender, n	
Male	60
Female	52
Age, mean±SD years	62.17±12.43
Smoking, n	
Nonsmoker or ex-smoker	68
Current smoker	44
ECOG performance status, n	
0 74	
1 or 2	38
Histology, n	
Adenocarcinoma (n=65)	
$TTF1^+$	59
$TTF1^-$	6
Non-adenocarcinoma (n=47)	
$TTF1^+$	0
$TTF1^-$	47
Stage, n	
I + II	16
III+ IV	96
Treatment, n	
Surgery	16
Chemotherapy	80
Radiation/chemoradiation	16
PFS, mean±SD months	7.32±6.34
OS, mean±SD months	15.14±13.74
SUV_m	30.95±20.67
SUV_{max}	46.27±31.00
MTV	21.53±26.31
TLG	823.5±149.24

mean±SD: Mean value±standard deviation, TTF1: Thyroid transcription factor-1; ECOG: Eastern Cooperative Oncology Group performance status; SUV_m: mean standardized uptake value; SUV_{max}: maximum standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis; OS: overall survival; PFS: progression-free survival.

Table II. *Clinical factors and positron-emission tomographic (PET) measurements associated with thyroid transcription factor-1 (TTF1) expression by non-small cell lung cancer(NSCLC) tumors.*

Factor	$TTF1^+$	$TTF1^-$	*p*-Value
Age (mean±SD), years	62.62±12.22	61.76±12.70	0.71
Gender, n			
Male	30	30	0.57
Female	29	23	
Histology, n			0.59
Adenocarcinoma	59	6	
Non-adenocarcinoma	0	47	
ECOG, n			0.69
0	40	34	
1 or 2	19	19	
Stage, n			0.43
I + II	10	6	
III + IV	49	47	
Treatment, n			0.19
Surgery	11	5	
Non-surgery	48	48	
PET measurement (mean±SD)			
SUV_m	22.98±2.5	32.24±4.17	0.71
SUV_{max}	34.14±3.71	42.67±6.10	0.06
MTV	19.55±4.9	24.38±4.41	0.06
TLG	425.92±9.24	1039.26±317.48	0.03
OS (mean±SD) months	20.22±2.61	13.28±2.30	0.05
PFS (mean±SD) months	11.47±2.07	5.42±1.69	0.03

mean±SD: Mean value±standard deviation, ECOG: Eastern Cooperative Oncology Group performance status, SUV_m: mean standardized uptake value, SUV_{max}: maximum standardized uptake value, MTV: metabolic tumor volume, TLG: total lesion glycolysis, OS: overall survival, PFS: progression-free survival. p-Values were calculated by the x^2 test and *t*-test.

The inclusion criteria were as follows: (i) the patient had no known history of cancer, (ii) the tumor was staged according to American Joint Cancer Committee (AJCC) 2002/2010 criteria (5), (iii) the patient was evaluated according to institutional guidelines, and (iv) the patient had undergone a subsequent clinical follow-up at our hospital. The pretreatment work-up consisted of a physical examination, evaluation of performance status, determination of complete blood counts and biochemistry profiles, and chest CT. Exclusion criteria were as follows: (i) no histopathologically confirmed NSCLC, (ii) small cell carcinoma or bronchial adenoma, (iii) no FDG-PET/CT before receiving any therapy, (iv) history of cancer, (v) lung cancer not staged according to the AJCC 2002/2010 criteria, (vi) lung cancer that was not diagnosed according to institutional guidelines, (vii) no subsequent clinical follow-up at our hospital, and (viii) administration of a steroid before the FDG-PET/CT examination. A total of 112 patients were included in the study.

Immunohistochemical staining. Formalin-fixed, paraffin-embedded sections were stained with TTF1 antibodies (clone 8G7G3/1; Neomarkers Co., Fremont, CA, USA). Immunohistochemical staining was performed using a streptavidinbiotin peroxidase system (DAKO LSAB kit, DAKO corporation, California, USA), and thyroid tissue was used as positive control for TTF1. Tumors were designated as being positive for TTF1 ($TTF1^+$) when their cells displayed a distinct brown nuclear staining. Immunostaining for TTF1 was semiquantitative and was independently scored by two pathologists; it was reported as the percentage of tumor cells with nuclear staining. Tumors were classified into three groups: a strongly positive group (++) in which 50% of the tumor cells were positive for TTF1; a weakly positive group+in which 49% of the tumor cells were positive for TTF1; and a negative group (−) in which fewer than 1% or none of the cells were positive for TTF1. Nuclear staining for TTF1 was subsequently categorized as negative (scores 0-1) or positive (score 2) based on tumor nuclei with unequivocal staining.

FDG-PET/CT analysis and measurement of tumor volume. Semi-quantitative and volumetric analyses of the primary tumors were performed using the volume viewer software on a GE Advantage Workstation 4.4 (GE Healthcare, Milwaukee, WI, USA), which provides a convenient and automatic means of delineating the volume

Table III. *Predictions of overall survival(OS) and progression free survival(PFS) based on clinical factors and positron-emission tomographic(PET) measurements in thyroid transcription factor-1 positive (TTF1⁺) and thyroid transcription factor-1 negative (TTF1⁻) tumors.*

	TTF1⁺ (n=59)				TTF1⁻ (n=53)			
Clinical factor	OS*	*p*-Value	PFS*	*p*-Value	OS*	*p*-Value	PFS*	*p*-Value
Age		0.14		0.04		0.06		0.00
≤75	31.11		31.51		28.91		29.95	
>75	20.17		16.67		18.80		14.30	
Gender		0.04		0.20		0.08		0.14
Female	34.60		32.90		31.24		30.61	
Male	25.50		27.20		23.75		24.33	
Histology		0.19		0.13		0.48		0.18
Adenocarcinoma	31.25		31.41		27.53		28.00	
Non-adenocarcinoma	23.06		22.17		22.83		19.17	
ECOG		0.47		0.71		0.89		0.15
0	31.11		29.43		27.21		29.29	
≥1	27.66		31.21		26.63		22.89	
Stage		0.00		0.00		0.00		0.00
I+II	45.67		46.67		44.40		45.65	
III+IV	24.62		24.49		27.06		26.85	
Treatment		0.00		0.00		0.01		0.01
Surgery	45.00		46.32		44.20		45.40	
Non-surgical	26.56		26.26		25.21		25.08	
PET measurement								
SUV_m		0.01		0.03		0.41		0.35
Low	32.22		31.03		31.39		31.63	
High	20.20		21.74		27.73		27.52	
SUV_{max}		0.00		0.00		0.21		0.19
Low	36.92		35.45		33.50		33.58	
High	20.98		21.88		27.50		27.51	
MTV		0.79		0.46		0.65		0.61
Low	26.42		28.60		28.56		28.44	
High	27.50		25.46		30.57		30.72	
TLG		0.01		0.00		0.51		0.34
Low	34.60		36.78		27.64		32.27	
High	22.39		21.08		30.64		27.81	

*Mean value. ECOG: Eastern Cooperative Oncology Group performance status, SUV_m: mean standardized uptake value, SUV_{max}: maximum standardized uptake value, MTV: metabolic tumor volume, TLG: total lesion glycolysis. p-Values were calculated by the Mann–Whitney test.

of interest using an isocontour threshold method based on the SUV. We placed the automatically delineated volume of interest over the primary lung lesion, and then the computer calculated the SUV_{max}, SUV_m, and MTV within the entire primary tumor. The MTV was defined as the total tumor volume greater than the threshold SUV of the mediastinal background SUV_m plus two standard deviations. We also calculated TLG as the product of MTV and SUV_m. The SUV was assigned an assumed default value of 1.0, which was the minimum value in all patients. The continuous PET parameters were examined for normality and skewness. A log2 transformation was applied to the skewed variables SUV_{max}, MTV, and TLG.

Statistical analysis. Progression-free survival was defined as the period extending from the date of FDG-PET until recurrence or final follow-up, and OS was defined as the period extending from the date of FDG-PET until death or final follow-up.

To obtain suitable cut-off points for age, TLG, MTV, SUV_m and SUV_{max}, receiver operating characteristic curves were used. Considering the adverse effects of aggressive therapy, we chose a high-specificity cut-off point of 95% with PFS as the outcome. Survival and PFS were calculated using the Kaplan–Meier method, and the groups were compared using the log-rank test. A multivariate analysis was performed with the Cox proportional hazards model to assess the joint effects and interactions of the following variables (relating to the primary tumor) on OS and PFS: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, histology, treatment modality, SUV_m, SUV_{max}, MTV, and TLG.

Results

Patients' characteristics. A total of 112 patients met the inclusion criteria. The clinicopathological characteristics of patients, are listed in Table I. Sixty of the patients were men and 52 women; their average age was 62.17±12.43 years.

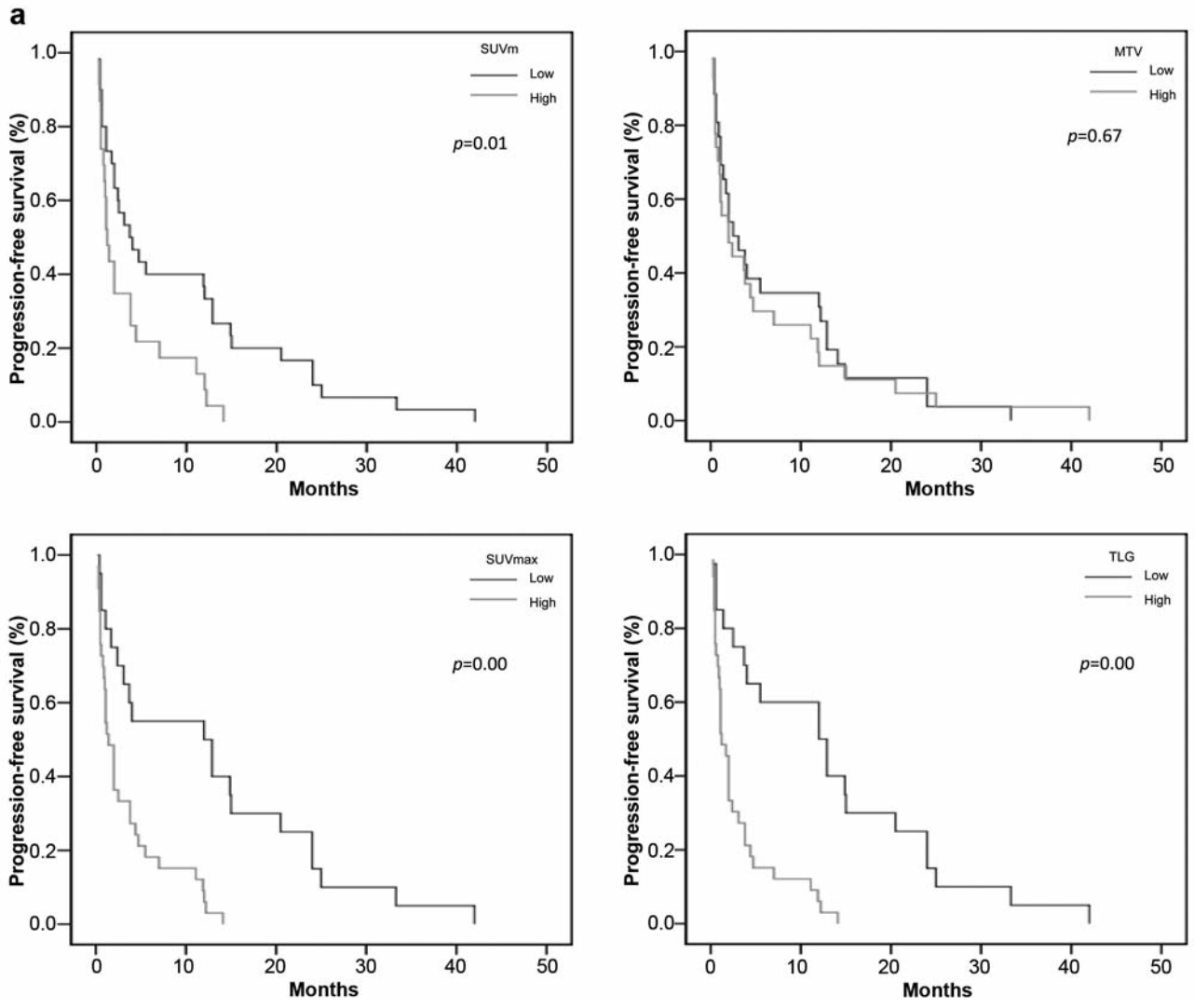

Figure 1. *Continued*

Sixty-five patients (58%) had adenocarcinoma, 59 (91%) of which were $TTF1^+$; 47 patients (42%) did not have adenocarcinoma and their tumors were not $TTF1^+$. The mean PFS was 7.32±6.34 months and the mean OS was 15.14±13.74 months. The mean PET SUV_m, SUV_{max}, MTV, and TLG values were 30.95±20.67, 46.27±31.00, 21.53±26.31, and 823.5±149.24, respectively.

FDG-PET values and TTF1 expression. The relationship between TTF1 expression and the available prognostic parameters is presented in Table II. The FDG uptake values were lower in patients with primary tumors that expressed TTF1. A significant association was only observed between TTF1 expression and TLG (p=0.03). The survival analysis showed that patients in the $TTF1^+$ group had a longer median PFS and OS than those in the $TTF1^-$ group (PFS: 11.47 *vs*. 5.42 months, p=0.03; OS: 20.22 *vs*. 13.28 months, p=0.05).

Prognostic value of FDG uptake. All FDG uptake values except for MTV, namely SUV_m, SUV_{max} and TLG, were significant prognostic factors among patients in the $TTF1^+$ group; however, none of these values was a significant prognostic indicator among patients in the $TTF1^-$ group (Table III).

Kaplan–Meier estimates of survival functions for PFS and OS are shown in Figures 1 and 2; FDG uptake by tumors

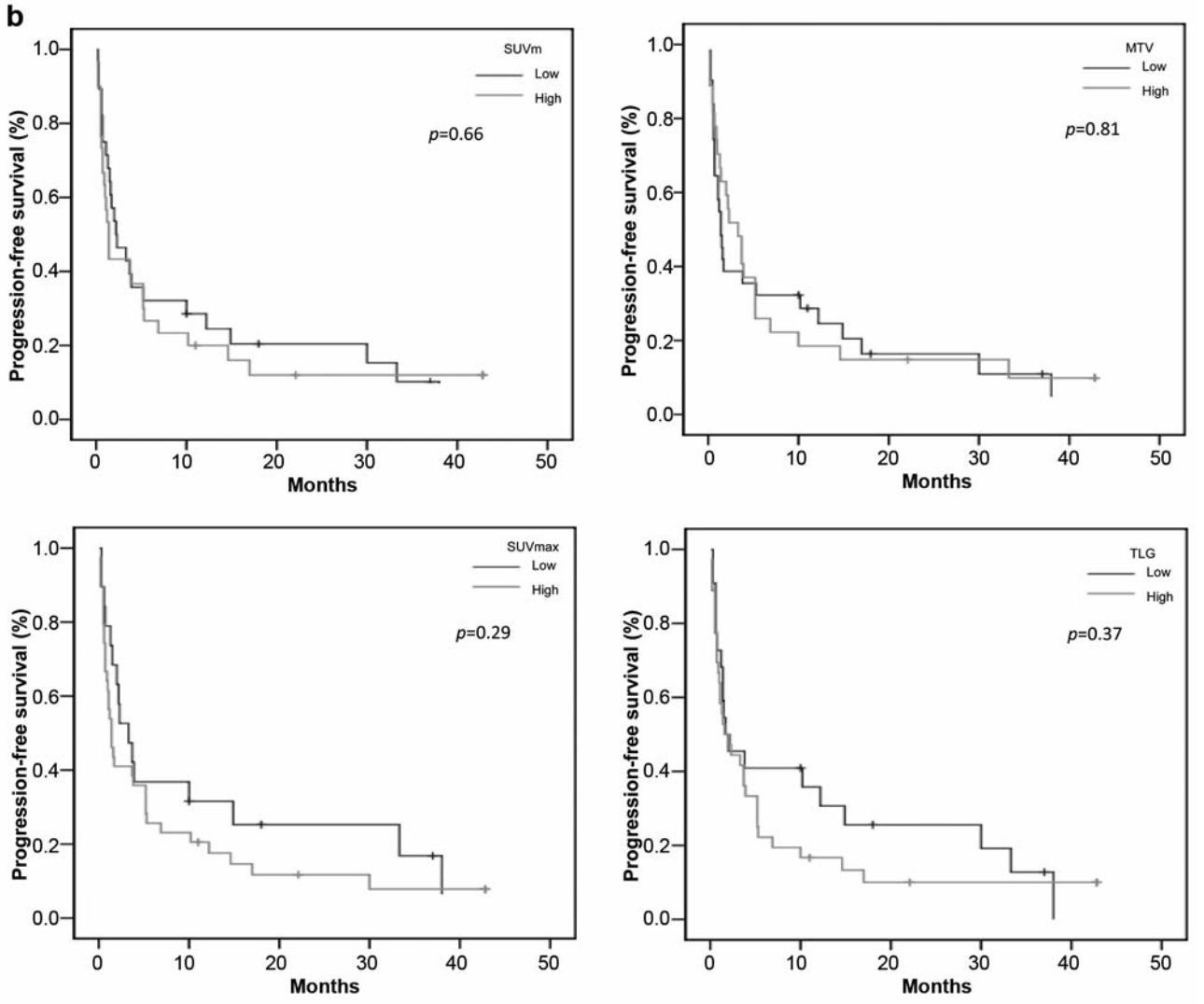

Figure 1. *Continued*

that did not express TTF1 was not significantly associated with PFS or OS.

We also conducted a Cox regression analysis incorporating FDG-PET parameters and found that SUV_m (p=0.01), SUV_{max} (p<0.001), and TLG (p<0.001) were significant predictors of PFS among patients in the $TTF1^+$ group (Table IV). In addition, SUV_m (p<0.001), SUV_{max} (p<0.001), and TLG (p<0.001) were significant predictors of OS among the same patients. However, these values were not significantly associated with PFS or OS among patients in the $TTF1^-$ group.

These findings suggest that assessment of FDG-PET values may be more useful for predicting PFS and OS among patients with tumors that express TTF1 compared with those with tumors that do not.

Discussion

Prognostic factors of lung cancer have been extensively studied and some clinical and biological parameters have been identified, primarily stage and ECOG performance status (6). Some have a direct impact on the therapeutic strategy, but a similar extent of disease can result in a different prognosis in different patients. There is, thus, a need to identify new prognostic factors. Recent studies have shown that FDG uptake by primary NSCLC tumors is an independent factor predictive of prognosis (7). Higher SUV_m, SUV_{max}, MRV, and TLG values are also observed in NSCLC with higher proliferation rates (8). However, many studies have shown that FDG uptake by the primary tumor is not correlated with prognosis (9-11).

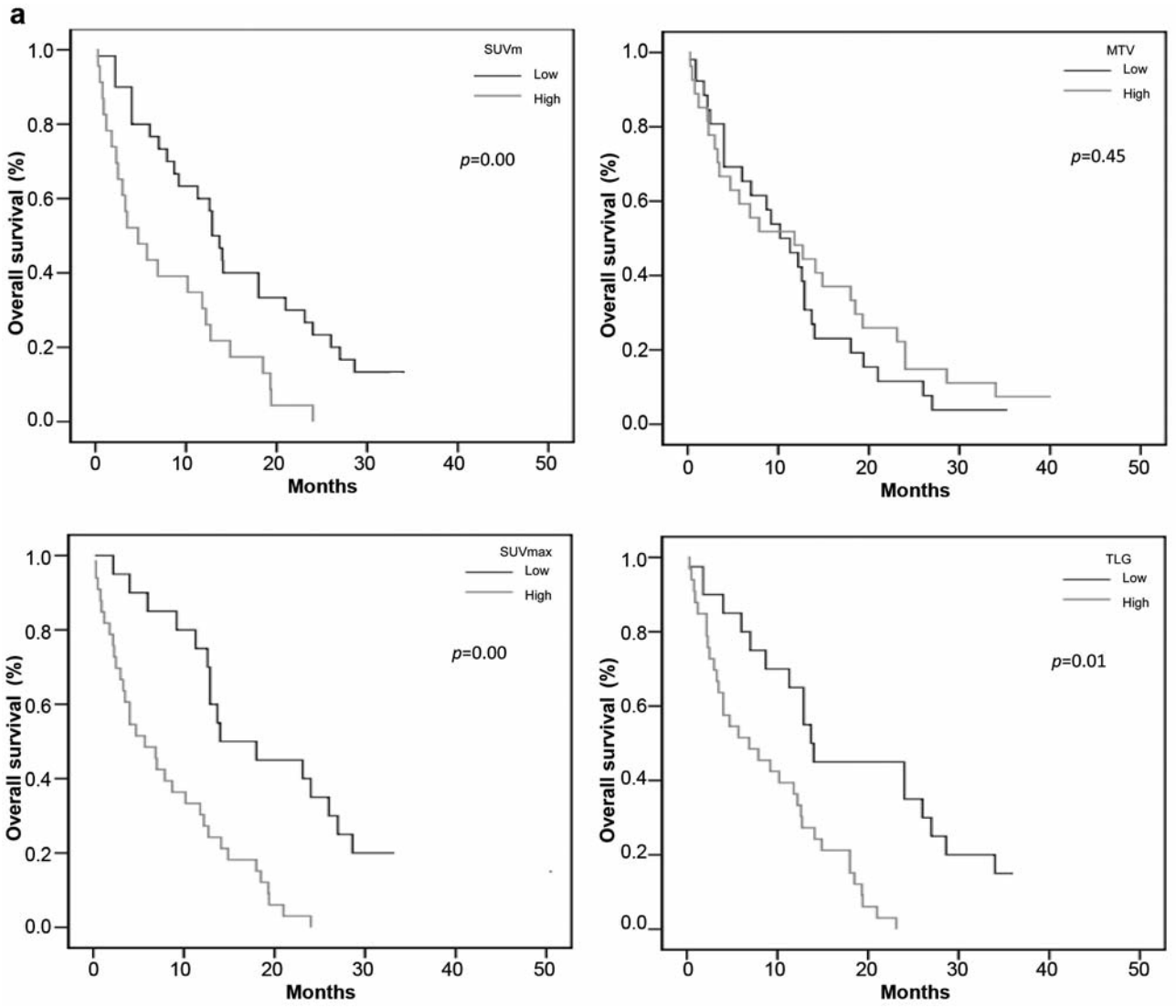

Figure 1. *Kaplan–Meier estimates of survival functions for progression free survival. Among patients in the thyroid transcription factor-1-positive TTF1+ group, survival functions differed significantly between those with higher and lower mean standardized uptake value SUVm (log-rank test, p=0.01), maximum standardized uptake value SUVmax (log-rank test, p<0.001), and total lesion glycolysis TLG (log-rank test, p<0.001) values, but there was no significant difference in relation to metabolic tumor volume MTV (log-rank test, p=0.67) (A). The FDG uptake by tumors that did not express TTF1 was not significantly associated with PFS (B).*

In the present study, we investigated the correlation between TTF1 expression and FDG uptake values and their effect on prognosis. We found that SUV_m, SUV_{max}, MTV, and TLG were lower in primary tumors that expressed TTF1. The survival analysis also showed that patients who had tumors with TTF1 expression had a longer median OS and PFS than those whose tumors did not express TTF1. Finally, we found that SUV_m, SUV_{max}, and TLG were only significant prognostic indicators among patients whose tumors expressed TTF1.

The prognostic role of TTF1 in survival has previously been assessed in a few studies that have primarily assessed local or locoregional stage NSCLC, but no study has assessed SUV_m, SUVx, MTV, or TLG (11). We found that FDG-PET may be more useful in patients with tumors that express TTF1 compared with those whose tumors do not, since OS and PFS can only be predicted by FDG uptake values in the former group.

Although little doubt remains that TTF1 expression portends a favorable prognosis in lung cancer, the mechanism responsible for this association remains

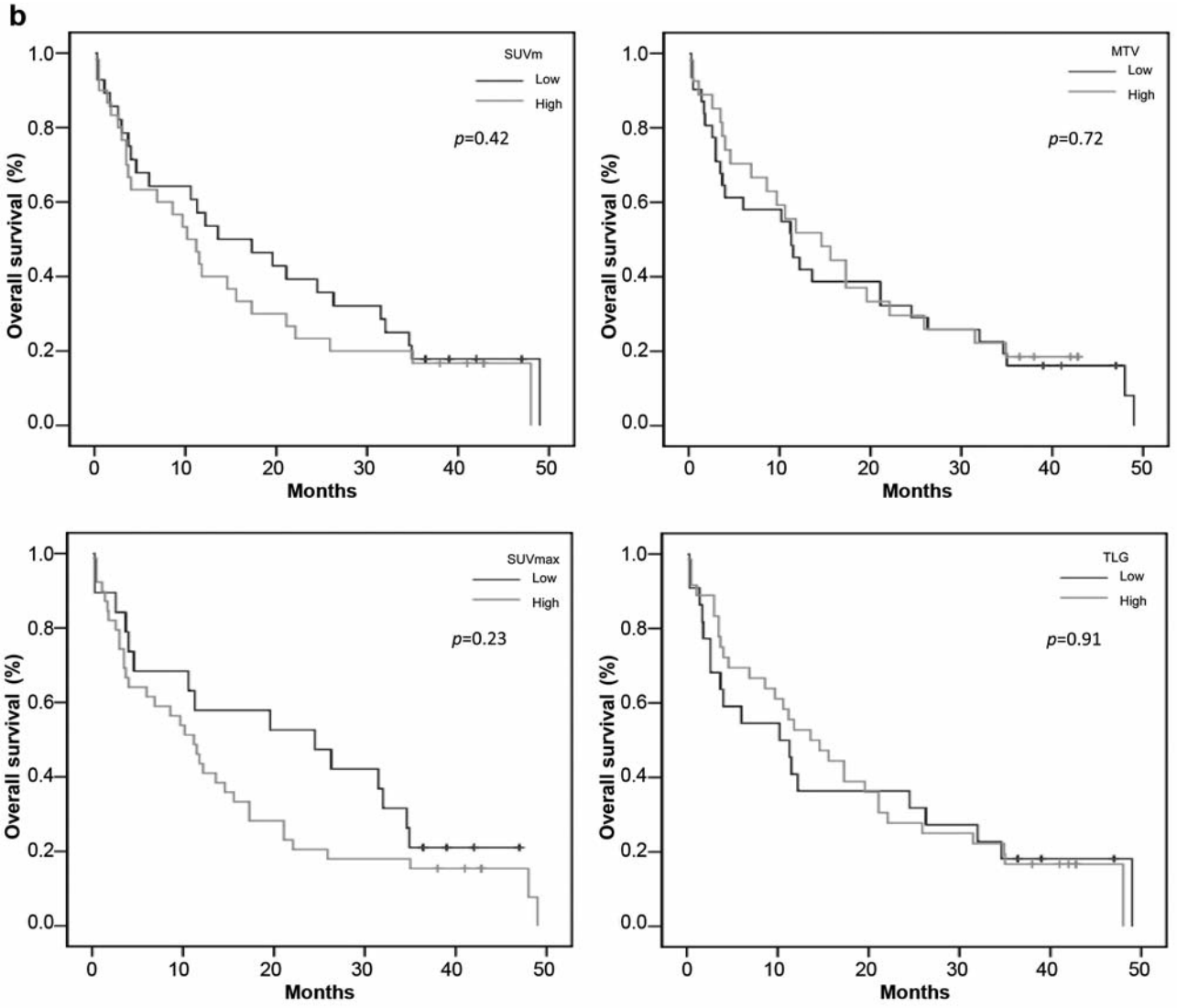

Figure 2. *Kaplan–Meier estimates of survival functions for overall survival (OS). As with the functions for PFS, there were significant differences in survival between individuals in the thyroid transcription factor-1-positive TTF1$^+$ group who had lower and higher mean standardized uptake value, SUVm (log-rank test, p<0.001), maximum standardized uptake value SUVmax (log-rank test, p<0.001), and total lesion glycolysis TLG (log-rank test, p=0.01) values. However, no such association was observed for metabolic tumor volume MTV (log-rank test, p=0.45) (A), indicating that SUVm, SUVmax, and TLG may all be useful for predicting the OS of patients with tumors that express TTF1. None of the FDG uptake values had a significant effect on the OS of patients in the TTF1$^-$ group (B), indicating that PET measurement may not suitable for predicting the OS of patients with lung cancer whose tumors do not express TTF1.*

unknown. Since TTF1 is normally expressed in the terminal respiratory unit, its presence within tumors could constitute a marker of retained differentiation and, consequently, a less aggressive phenotype (12). Alternatively, the predictive value of TTF1 expression could reflect underlying associated pathways that carry their own prognostic implications based on less aggressive disease. Improved responsiveness to available treatment regimens and a better prognosis have also been noted.

Our study has several limitations. Firstly, the lesions were defined by using a threshold method. The choice of threshold will influence on the measurement of tumor volume, SUV_m, and whole-body TLG. Because no single optimal threshold can provide accurate tumor delineation, we used a commonly adopted percentage threshold (namely 50% of SUV_{max}) to determine the tumor volume and then checked the results with fused CT images to decide if further adjustment of the threshold was needed (13, 14). Currently, several methods of

Table IV. *Cox regression analysis findings relating to overall survival (OS) and progression free survival (PFS) based on thyroid transcription factor-1 (TTF1) expression.*

Groups/factors	OS		PFS	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
TTF1 (+) group				
Age	1.56 (0.68-0.36)	0.24	2.46 (1.05-5.76)	0.04
Gender	1.13 (0.65-1.99)	0.66	1.41 (0.80-2.48)	0.24
Histology	1.05 (0.42-2.67)	0.91	0.98 (0.38-2.55)	0.97
ECOG	0.96 (0.54-1.72)	0.89	1.69 (0.94-3.03)	0.08
Stage	3.02 (1.17-7.78)	0.02	3.72 (1.44-9.59)	0.01
Treatment	2.12 (0.83-5.46)	0.11	2.40 (0.94-6.16)	0.07
PET measurement				
SUV_m	2.46 (1.36-4.45)	0.00	2.24 (1.23-4.08)	0.01
SUV_{max}	3.51 (1.82-7.00)	0.00	3.63 (1.79-7.37)	0.00
MTV	0.81 (0.46-1.42)	0.46	1.12 (0.65-1.94)	0.68
TLG	3.30 (1.63-6.69)	0.00	4.28 (2.10-8.74)	0.00
TTF1 (–) group				
Age	2.97 (1.08-8.18)	0.04	5.31 (1.84-15.34)	0.00
Sex	1.71 (0.89-3.29)	0.10	1.36 (0.75-2.46)	0.32
Histology	1.45 (0.66-3.20)	0.35	2.45 (1.04-5.79)	0.05
ECOG	1.39 (0.69-2.77)	0.35	0.66 (0.33-1.31)	0.24
Stage	1.89 (0.81-4.27)	0.13	2.21 (0.93-5.24)	0.07
Treatment	1.72 (0.68-4.36)	0.25	1.55 (0.82-2.96)	0.18
PET measurement				
SUV_m	1.05 (0.44-2.51)	0.91	0.75 (0.33-1.71)	0.50
SUV_{max}	1.61 (0.64-4.00)	0.31	1.44 (0.61-3.39)	0.41
MTV	1.02 (0.51-2.07)	0.94	0.76 (0.37-1.55)	0.45
TLG	0.75 (0.32-1.74)	0.49	1.54 (0.68-3.51)	0.30

PET: Positron emission tomography, TTF1: thyroid transcription factor-1, Adeno Adenocarcinoma, Non-Adeno Non-Adenocarcinoma, ECOG: Eastern Cooperative Oncology Group Performance Status, SUV_m: mean standardized uptake value, SUV_{max}: maximum standardized uptake value, MTV: metabolic tumor volume, TLG: total lesion glycolysis, OS: overall survival, PFS: progression free survival.

delineating tumor volumes on PET images have been proposed, but further validation of these methods is required. If a better PET tumor delineation method is adopted, TLG might be able to provide even better prognostic information. Secondly, high FDG accumulation is not limited to malignant tissues. Indeed, higher FDG uptake has been shown in tumor-associated macrophages and young granulation tissues compared to tumor cells (15, 16). Thus, FDG uptake may be overestimated. Thirdly, this was a retrospective study with a relatively small number of patients. A larger, multi-Institutional, prospective, and randomized study is needed to validate the current findings.

In conclusion, NSCLC tumors that express TTF1 have lower FDG uptake values. A low TLG value in a primary tumor that expresses TTF1 is associated with better PFS. However, FDG uptake values might be misinterpreted and used incorrectly as a prognostic factor in NSCLC tumors that do not express TTF1.

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