Prognostic Value of Tumor-to-Blood Standardized Uptake Ratio in Patients with Resectable Non-Small-Cell Lung Cancer

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Abstract

Objectives Previously published studies showed that the standard tumor-to-blood standardized uptake value (SUV) ratio (SUR) was a more accurate prognostic method than tumor maximum standardized uptake value (SUV_{max}). This study evaluated and compared prognostic value of positron emission tomography (PET) parameters and normalized value of PET parameters by blood pool SUV in non-small-cell lung cancer (NSCLC) patients who received curative surgery.

Methods Seventy-seven patients who underwent curative resection for NSCLC between January 2010 to December 2013 were enrolled in this study. ¹⁸Fluorine-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT) was performed before surgery. The mean standardized uptake value (SUV_{mean}), SUV_{max}, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of each lesion was measured, on the workstation. SUR_{mean}, SUR_{max},

and TLGSUR were calculated by dividing each of them by descending aorta SUV_{mean}. Cox proportional hazards regression was used to analyze the effect of age, sex, pathological parameters, and PET parameters on recurrence and death.

Results In Cox regression analysis, N stage predicted for both recurrence ($p < 0.0001$) and death ($p < 0.0001$). SUR_{max} predicted recurrence ($p = 0.0014$), not death. Area under the receiver operating characteristic curve of SUR_{max} was 0.759 with cutoff value 4.004. However, SUV_{max}, SUV_{mean}, MTV, TLG, SUR_{mean}, and TLGSUR predicted neither recurrence nor death.

Conclusions Among PET parameters, SUR_{max} was the independent predictor of recurrence in NSCLC patients who received curative surgery. N stage was the independent prognostic factor for both recurrence and death. Both parameters could be used to stratify the risk of NSCLC patients.

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Introduction

Lung cancer is the third most commonly diagnosed cancer and the most common cause of cancer death in Korea. The 5-year survival rate for lung cancer is 21.9 % [1]. Non-small-cell lung cancer (NSCLC) comprises about 85 % of all lung cancer [2]. In early NSCLC patients, lobectomy is standard treatment, and patients who are not candidates for surgery have to receive a radiotherapy [3]. In advanced stage, chemotherapy or concomitant chemoradiotherapy are considered as the standard treatment [2, 3]. Therefore, precise staging in patients with NSCLC is important.

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^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) is used in staging, surveillance, radiation therapy planning, and predicting prognosis in lung cancer [4]. Research shows that PET parameters could represent the activity of tumor. Of the PET parameters, the maximum standardized uptake value (SUV_{max}) is commonly used to report tumor activity. It has a high reproducibility and a low interobserver variability [5]. As SUV_{max} is defined by the highest voxel value within the region of interest (ROI), it is sensitive to image noise [5]. Therefore, mean standardized uptake value (SUV_{mean}) is important to report tumor activity. As metabolic tumor volume (MTV) represents the amount of high metabolic tumor cells [6] and total lesion glycolysis (TLG) represents tumor size and degree of ^{18}F -FDG [7], MTV and TLG have been proposed for risk stratification of lung cancer. MTV is defined as a volume of the tumor, delineated by a specific threshold of SUV. TLG is derived by multiplying MTV and SUV_{mean} , and represents tumor burden [8]. MTV and TLG are predictive of overall survival (OS) and recurrence in NSCLC [8, 9].

A recent study has proved that tumor-to-blood SUV ratio (SUR), the ratio of tumor SUV and aorta blood SUV, showed a stronger correlation with the metabolic rate of FDG than tumor SUV [10]. In a subsequent study, SUR of esophageal carcinoma was an independent prognostic factor of OS and distant metastasis-free survival [11]. Therefore, the aim of this study was to evaluate and compare prognostic value of positron emission tomography (PET) parameters and normalized value of PET parameters by blood pool SUV in non-small-cell lung cancer (NSCLC) patients who received curative surgery.

Materials and Methods

Patients

Three thousand one hundred forty patients were registered as a lung cancer between January 2010 to December 2013. Inclusion criteria were patients with 1) pathologically confirmed NSCLC (adenocarcinoma and squamous cell carcinoma) and 2) preoperative ^{18}F -FDG PET/CT. Exclusion criteria were patients who 1) received chemotherapy, radiation therapy, or concurrent chemoradiation therapy without surgery, 2) had distant metastasis confirmed by imaging modalities such as chest CT, brain magnetic resonance imaging, bone scintigraphy, and ^{18}F -FDG PET/CT, 3) did not perform ^{18}F -FDG PET/CT at staging, 4) had not enough medical records. Seventy-seven patients met the criteria and they were enrolled in this study. The median follow-up was 33 months and the follow-up ranged from 2 month to 64 month. The endpoint of study was 15 August 2015. Our institutional review board waived informed consent and approved the study.

^{18}F -FDG PET/CT Imaging

According to the standard protocol of our institution, all patients fasted for at least 6 h. Their median blood glucose level was 98 mg/dl (range: 66–143 mg/dl) before ^{18}F -FDG administration. Sixty minutes after injection of 0.14 mCi/kg ^{18}F -FDG, PET/CT scans were performed (Biograph 40, Siemens, Knoxville, TN, USA). Low-dose CT from the base of the skull to the proximal thighs was performed for the purpose of attenuation correction and precise anatomical localization. PET data were obtained using a high-resolution whole-body scanner. The scan time per bed position was two minutes with 500 mm axial field of view. Reconstruction parameters were iterative reconstruction with three iterations, 21 subsets; Gaussian smoothing filter with image size 168; voxel dimension 3.9×3.9 mm.

Image Analysis

PET/CT images were interpreted directly from the workstation (Siemens TrueD image analysis software, Siemens, Knoxville, TN, USA). A volume of interest (VOI) was drawn over the entire abnormal uptake of lung cancer to include a large amount of radioactivity on axial images semi-automatically. SUV_{max} of ^{18}F -FDG was measured from VOI. SUV_{mean} and MTV of each lesion were calculated automatically on the workstation and SUV 2.5 was adopted as the threshold. TLG was calculated by multiplying SUV_{mean} by MTV. Blood SUV_{mean} was measured from VOI in the descending aorta (Fig. 1). SUR was derived from the value of SUV_{max} , SUV_{mean} , and TLG divided by blood SUV_{mean} (Eq. 1). The method of delineation of aorta and calculation of SUR followed published research [11].

$$\begin{aligned}\text{SUR}_{\text{max}} &= \frac{\text{Tumor SUV}_{\text{max}}}{\text{Blood SUV}_{\text{mean}}} \\ \text{SUR}_{\text{mean}} &= \frac{\text{Tumor SUV}_{\text{mean}}}{\text{Blood SUV}_{\text{mean}}} \\ \text{TLG SUR} &= \frac{\text{Tumor TLG}}{\text{Blood SUV}_{\text{mean}}}\end{aligned}\quad (1)$$

Statistical Analysis

Cox proportional hazards regression was used to analyze the effect of age, sex, pathological parameters such as histopathologic class, pathologic T stage, nodal involvement and stage, and PET parameters on recurrence and death. Recurrence was defined as a tumor recurrence including local recurrence, regional recurrence, and distant metastasis identified by imaging study. The date of death was obtained from patient's medical records. Two-sided null hypotheses of no difference were

Fig. 1 Delineation of aorta. Delineation was performed on fusion view and was checked by both attenuation CT and PET image

rejected if p -values were less than or equal to 0.05 and the 95 % confidence of intervals do not cross 1. Receiver operating characteristic (ROC) curves of PET parameters were drawn and compared to evaluate the capability to predict recurrence and death. The predictive value of the PET parameters was assessed by the area under curve (AUC) of the ROC curve. Recurrence free survival (RFS) was defined as the interval from the operation date to the date of recurrence identified by imaging study or last clinical follow-up and Kaplan–Meier survival analysis with log-rank test was performed according to PET parameters. The cutoffs were determined by median values of each PET parameter. Data analysis was performed by MedCalc v.15.11 software (MedCalc, Mariakerke, Belgium).

Results

Patient Characteristics

Seventy-seven NSCLC patients were included in this study. Patient characteristics are shown in Table 1. The mean age was 62.4 ± 8.7 years. Lymph node metastasis was present in 20 patients (26 %). Eighteen patients (23.4 %) had experienced recurrence and four patients (5.2 %) died during the follow-up (34.0 ± 14.7 months). Median OS and RFS were 34 and 33 months, respectively. The difference of OS and RFS was small. It could be due to short follow-up period or the majority of patients had early stage. The mean value of SUV_{mean} , SUV_{max} , MTV, TLG, SUR_{mean} , SUR_{max} , and TLGSUR were 4.174 ± 1.847 , 8.748 ± 5.863 , 17.670 ± 28.210 ml, 105.692 ± 190.515 g, 1.937 ± 0.904 , 4.024 ± 2.730 , and 49.834 ± 96.569 , respectively.

Recurrence

N stage (hazard ratio 2.508, 95 % CI 1.499–4.197, $p = 0.0005$), TNM stage (2.382, 1.362–4.163, $p = 0.0023$), SUR_{max} (1.277, 1.099–1.484, $p = 0.0014$), SUR_{mean} (2.299, 1.390–3.802, $p = 0.0012$), SUV_{max} (1.113, 1.039–1.192, 0.0022), SUV_{mean} (1.472, 1.163–1.864, $p = 0.0013$), TLGSUR (1.0051, 1.002–1.009, $p = 0.0057$), MTV (1.014, 1.001–1.027, $p = 0.0377$), and TLG (1.003, 1.001–1.004, $p = 0.0076$) predicted recurrence in univariate analysis (Table 2). Age (1.109, 1.037–1.187, $p < 0.0027$), N stage (3.381, 1.934–5.910, $p < 0.0001$), and SUR_{max} (1.381, 1.132–1.685, $p = 0.0014$) predicted recurrence

in multivariate analysis (Table 2). AUC of SUR_{max} , SUR_{mean} , TLGSUR, MTV, SUV_{max} , SUV_{mean} , and TLG were 0.759, 0.735, 0.686, 0.664, 0.744, 0.759, and 0.682, respectively. Although SUR_{max} and SUV_{mean} had higher AUC among the PET parameters, there were no PET parameters which had significantly higher AUC values. AUC of PET parameters for predicting recurrence are in Table 3. Kaplan–Meier survival analysis with log-rank test is in Fig. 2. The cutoff values of PET parameters were derived from median value. SUR_{max} ($p = 0.0073$), SUR_{mean} ($p = 0.0091$), TLGSUR ($p = 0.0077$), SUV_{max} ($p = 0.0016$), and SUV_{mean} ($p = 0.0024$) showed significant difference in recurrence.

Death

TNM stage (4.975, 1.249–19.819, $p = 0.0229$) and SUV_{max} (1.152, 1.001–1.326, $p = 0.0485$) predicted death in univariate analysis (Table 4). N stage (3.868, 1.536–9.742, $p = 0.0041$)

Table 1 Patient characteristics

Variables	Value (%)
Age (years)	
Mean $\pm$ SD	62.4 ± 8.7
Sex	
Male	46 (59.7)
Female	31 (40.3)
Histology	
Squamous cell carcinoma	21 (27.3)
Adenocarcinoma	56 (72.7)
T stage	
T1	41 (53.2)
T2	29 (37.7)
T3	6 (7.8)
T4	1 (1.3)
N stage	
N0	57 (74.0)
N1	11 (14.3)
N2	8 (10.4)
N3	1 (1.3)
TNM stage	
I	48 (62.3)
II	19 (24.7)
III	10 (13.0)
IV	0 (0)

Table 2 Univariate and multivariate analysis of recurrence

Variables	Wald	Univariate			Wald	Multivariate		
		HR	95 % CI	P		HR	95 % CI	P
Age	2.6356	1.0487	0.9902–1.1106	0.1045	8.9980	1.1091	1.0365–1.1867	0.0027
Sex	0.9616	0.6115	0.2288–1.6342	0.3268				
T stage	1.6061	1.5433	0.7889–3.0194	0.2050				
N stage	12.2522	2.5080	1.4987–4.1970	0.0005	18.2661	3.3807	1.9338–5.9104	<0.0001
TNM stage	9.2705	2.3815	1.3622–4.1632	0.0023				
Histology	0.06011	1.1378	0.4054–3.1936	0.8063				
SUR _{max}	10.2321	1.2772	1.0994–1.4838	0.0014	10.1456	1.3814	1.1323–1.6853	0.0014
SUR _{mean}	10.5215	2.2990	1.3902–3.8019	0.0012				
TLGSUR	7.6536	1.0051	1.0015–1.0088	0.0057				
MTV (ml)	4.3170	1.0136	1.0008–1.0266	0.0377				
SUV _{max}	9.3900	1.1130	1.0393–1.1919	0.0022				
SUV _{mean}	10.3519	1.4724	1.1632–1.8637	0.0013				
TLG (g)	7.1288	1.0025	1.0007–1.0044	0.0076				

SUR: standard tumor-to-blood SUV ratio; SUV_{max}: maximum standardized uptake value; SUV_{mean}: mean standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis

was the only parameter which showed significance both in univariate and multivariate analysis (Table 4). AUC of SUR_{max}, SUR_{mean}, TLGSUR, MTV, SUV_{max}, SUV_{mean}, and TLG were 0.781, 0.729, 0.777, 0.764, 0.812, 0.812, and 0.788, respectively. Although SUV_{max} and SUV_{mean} had higher AUC among the PET parameters, there were no PET parameters which had significantly higher AUC values. AUC of PET parameters for predicting death are shown in Table 5.

Discussion

In this study, SUR_{max}, age, and N stage were independent prognostic factors for recurrence in NSCLC patients. N stage was the only independent prognostic parameter for death.

Several studies showed that age was a prognostic factor in lung cancer [12, 13], while other studies did not [14, 15]. In

this study, age was an independent prognostic factor for recurrence. The difference of results could be due to different composition of staging, various histology, and different definition of older patient.

TNM staging is the most widely accepted prognostic factor for risk stratification [16]. In this study, N stage was the independent factor for both recurrence and death. However, T stage did not show the significance of prognostic value. It might be due to the fact that the distribution of T stage was biased toward early stage.

Previous studies have presented that SUV_{max} was a prognostic factor for lung cancer [17]. However, according to Chen et al.'s study, SUV_{max} did not predict progression free survival independently, which was consistent with our results [18]. As SUV_{max} is the highest voxel value within the ROI, it is independent of ROI definition [5, 19]. However, it is more susceptible to noise and cannot reflect metabolic activity of

Table 3 Area under the ROC curve (AUC) of PET parameters for predicting recurrence

Parameters	Cutoff	AUC	95 % CI	Sen	Sp	LR+	LR-	p-value
SUR _{max}	>4.004	0.759	0.648–0.849	83.33	66.10	2.46	0.25	<0.0001
SUR _{mean}	>1.9757	0.735	0.623–0.829	77.78	64.41	2.19	0.35	0.0004
TLGSUR	>11.7338	0.686	0.571–0.787	77.78	59.32	1.91	0.37	0.0077
MTV (ml)	>4.24	0.664	0.548–0.768	77.78	50.85	1.58	0.44	0.0211
SUV _{max}	>9.46	0.744	0.632–0.837	83.33	66.10	2.46	0.25	0.0001
SUV _{mean}	>4.41	0.759	0.648–0.850	83.33	69.49	2.73	0.24	<0.0001
TLG (g)	>22.6476	0.682	0.566–0.783	77.78	55.93	1.76	0.40	0.0110

SUR: standard tumor-to-blood SUV ratio; SUV_{max}: maximum standardized uptake value; SUV_{mean}: mean standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis; Sen: sensitivity; Sp: specificity; LR: likelihood ratio

Fig. 2 Kaplan–Meier curve depicting the recurrence free survival according to SUR_{max} (a), SUR_{mean} (b), $TLGSUR$ (c), SUV_{max} (d), SUV_{mean} (e), and TLG (f)

the whole tumor volume [5, 19]. As SUV_{max} is limited in representing tumor metabolic activity, MTV and TLG are proposed for risk stratification of lung cancer [8]. MTV and TLG represent both the degree of ^{18}F -FDG uptake and the size of the tumor [8]. However, MTV is dependent on cutoff values, and it might include inflammation around primary cancer [20]. Therefore, MTV and TLG have weaknesses. Although several studies of volumetric parameters showed association

with prognosis in NSCLC patients [8, 9], MTV and TLG were not independent prognostic factors for recurrence in this study. Two thirds of patients who enrolled in this study were stage I and the median follow-up was 33 months. This could influence the results.

Although SUV_{max} has a high reproducibility, it can vary between different PET scanners [21]. To overcome this shortcoming, tumor SUV is commonly normalized by

Table 4 Univariate and multivariate analysis of death

Variables	Wald	Univariate			Wald	Multivariate		
		HR	95 % CI	P		HR	95 % CI	P
Age	0.3919	1.0396	0.9206–1.1740	0.5313				
Sex	NA	NA	NA	NA				
T stage	1.4233	1.9410	0.6529–5.7702	0.2329				
N stage	8.2404	3.8681	1.5359–9.7418	0.0041	8.2404	3.8681	1.5359–9.7418	0.0041
TNM stage	0.7052	4.9754	1.2490–19.8191	0.0229				
Histology	1.2138	3.0148	0.4233–21.4729	0.2706				
SUR_{max}	3.0615	1.3183	0.9673–1.7967	0.0802				
SUR_{mean}	1.6479	1.9075	0.7116–5.1128	0.1992				
$TLGSUR$	1.2348	1.0044	0.9967–1.0121	0.2665				
MTV (ml)	2.0618	1.0189	0.9932–1.0453	0.1510				
SUV_{max}	3.8934	1.1522	1.0009–1.3262	0.0485				
SUV_{mean}	2.7871	1.5047	0.9314–2.4310	0.0950				
TLG (g)	1.5973	1.0025	0.9986–1.0064	0.2063				

SUR : standard tumor-to-blood SUV ratio; SUV_{max} : maximum standardized uptake value; SUV_{mean} : mean standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis; NA: not applicable

Table 5 Area under the ROC curve (AUC) of PET parameters for predicting death

Parameters	Cutoff	AUC	95 % CI	Sen	Sp	LR+	LR-	p-value
SUR _{max}	>4.0359	0.781	0.672–0.867	100.0	58.90	2.43	0	0.0007
SUR _{mean}	>1.9757	0.729	0.616–0.824	100.0	57.53	2.35	0	0.0011
TLGSUR	>15.3114	0.777	0.668–0.864	100.0	60.27	2.52	0	0.0005
MTV (ml)	>7.74	0.764	0.653–0.853	100.0	57.53	2.35	0	0.0211
SUV _{max}	>10	0.812	0.706–0.892	100.0	61.64	2.61	0	0.0001
SUV _{mean}	>4.88	0.812	0.706–0.892	100.0	73.97	3.84	0	<0.0001
TLG (g)	>37.2068	0.788	0.680–0.873	100.0	60.27	2.52	0	0.0006

SUR: standard tumor-to-blood SUV ratio; SUR_{max}: maximum standardized uptake value; SUR_{mean}: mean standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis; Sen: sensitivity; Sp: specificity; LR: likelihood ratio

liver activity. SUV of the normal human liver remains constant if the time delay between tracer injection and PET acquisition is in the range of 50–110 min [22]. Therefore, it can be a reference organ to interpret PET scan [22]. Tumor SUR_{max} normalized to liver can predict prognosis in various malignancies including NSCLC [23–25]. However, according to Besson et al., SUV of the liver was significantly different between giant cell arteritis patients and control patients [26]. Systemic inflammation affects liver metabolism and can influence the liver uptake ratio [26].

According to the study of Hoff et al., inter-study variability of the arterial input function (AIF) was a crucial factor adversely affecting the correlation between SUV and Km (the metabolic rate of glucose consumption) [10]. As the equation of SUR derived from Patlak formula was less dependent on AIF than the equation of SUV, they expected that SUR had higher linear correlation to Km than SUV and validated their theory by colorectal cancer patients with fully dynamic investigations [10]. As a subsequent study, Butoff et al. showed that SUR was an independent prognostic factor for OS and distant metastasis (DM) in esophageal cancer [11]. In their study, MTV was also an independent prognostic factor for OS and DM. However, the hazard ratio of SUR was higher than MTV [11]. This study demonstrated that SUR_{max} was an independent prognostic factor for recurrence, consistent with previous study.

This study had several limitations. First, it was designed as a retrospective observational study. Second, a small number of patients were included. Third, follow up period was short. Fourth, partial volume effect correction for lung cancer was not performed.

In conclusion, SUR_{max} was the independent prognostic factor for recurrence among the PET parameters in NSCLC patients, while N stage was the independent prognostic factor for both recurrence and death. Both SUR_{max} and N stage could be used to stratify the risk of NSCLC patients. Since this study was

retrospective with small sample size, further prospective and larger study should be performed to validate this result.

Acknowledgments The manuscript has not been published before or is not under consideration for publication anywhere else and has been approved by all co-authors.

Compliance with Ethical Standards

Conflict of Interest Seunghyeon Shin, Seong-Jang Kim, In Joo Kim, Kyoungjune Pak and Bum Soo Kim declare that they have no conflict of interest.

Ethical Statement The study was approved by an institutional review board or equivalent and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All subjects in the study gave written informed consent or the institutional review board waived the need to obtain informed consent.

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