

Metabolic tumor volume on FDG-PET/CT is a possible prognostic factor for Stage I lung cancer patients treated with stereotactic body radiation therapy: a retrospective clinical study

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ABSTRACT

The aim of this study was to determine whether metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are associated with outcomes in Stage I lung cancer patients treated with stereotactic body radiation therapy (SBRT). Thirty-eight patients underwent [¹⁸F] fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) within 60 days before SBRT at our institution between January 2001 and December 2011. The maximum standardized uptake value (SUV_{max}), MTV₂, MTV₄, MTV₆, TLG_{40%}, TLG_{50%} and TLG_{60%} were calculated. Prognostic factors for overall survival (OS) and local control (LC) were analyzed using Cox's proportional hazards model, and survival curves were calculated using the Kaplan–Meier method. Receiver operating characteristics (ROC) curves of PET parameters for OS and LC were calculated. The median follow-up period for survivors was 37.7 months. Three-year OS and LC rates were 56.4% and 70.5%, respectively, and 5-year OS and LC rates were 36.8% and 70.5%, respectively. In univariate analyses, tumor diameter ($P = 0.019$), single dose ≥ 10 Gy ($P = 0.017$), MTV₂ ($P = 0.030$) and MTV₄ ($P = 0.048$) were significant predictors for OS. Tumor diameter ($P < 0.001$), single dose ≥ 10 Gy ($P = 0.007$), SUV_{max} ($P = 0.035$), MTV₂ ($P < 0.001$), MTV₄ ($P = 0.003$), MTV₆ ($P = 0.017$), TLG_{40%} ($P < 0.001$), TLG_{50%} ($P = 0.001$) and TLG_{60%} ($P = 0.003$) were significant predictors for LC. SUV_{max} was not a significant predictor for OS. We made the ROC curves at PET parameters, and the largest area under the curve value for OS was MTV₂ and for LC was TLG_{40%}. Tumor diameter, single dose ≥ 10 Gy, MTV₂ and MTV₄ are prognostic factors for OS and LC rates and MTV₂ is a better prognostic factor for OS than other PET parameters.

KEYWORDS: stereotactic body radiation therapy, non-small cell lung cancer, NSCLC, metabolic tumor volume, total lesion glycolysis, prognostic factor

INTRODUCTION

Surgery has been the standard treatment for early-stage non-small cell lung cancer (NSCLC). In recent times, patients who are medically inoperable because of comorbidities or because they have rejected surgery are being treated with stereotactic body radiation therapy (SBRT). Good local control (LC) rates have been achieved with SBRT for inoperable patients [1]. A good overall survival (OS) rate has also been achieved with SBRT for operable patients with Stage I NSCLC [2].

Positron emission tomography-computed tomography using ¹⁸F-fluorodeoxyglucose (FDG-PET/CT) is used to search for lymph node metastases and distant organ metastases, and the use of FDG-PET/CT has improved the rate of detection of these metastases in patients with NSCLC [3]. The SUV_{max} is mainly used as a measure of malignancy, but it is controversial whether SUV_{max} is a prognostic factor for Stage I NSCLC treated with SBRT [4]. Therefore, another parameter in FDG-PET/CT as a prognostic factor is required. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been reported as possible prognostic factors [5–7].

In this study, we investigated whether pretreatment MTV and TLG were associated with LC rates and OS in patients with Stage I NSCLC treated with SBRT.

MATERIALS AND METHODS

Patients

We retrospectively reviewed a clinical database of patients with Stage I primary lung cancer treated by SBRT in our institution between January 2001 and December 2011. A total of 80 patients with 82 lesions received FDG-PET/CT before SBRT, and data for 47 of those patients with 48 lesions were available to measure metabolic parameters. Standardized uptake value data before December 2004, except for the SUV_{max} written in the report, had already been deleted. We excluded patients for whom more than 60 days had passed from FDG-PET/CT to the first day of SBRT. Finally, 38 patients were included in this study.

The patients' characteristics and irradiation dose characteristics are summarized in Table 1. The median age of the patients was 77 years (range, 48–88 years). Twenty-six lesions were pathologically proven, but 12 lesions were not proven. The median tumor diameter was 2.3 cm (range, 0.9–4.2 cm). All lesions were of peripheral type.

SBRT procedure

The SBRT technique used in our institution has been reported several times [8–9]. The treatment procedure is summarized in Table 2. We observed respiratory-driven tumor motion on a simulator (Ximatron, Varian Medical Systems). When respiratory motion was large, we used an abdominal pressure belt.

The gross tumor volume (GTV) was defined as the visible extent of the tumor on a CT image with a pulmonary window. The clinical target volume (CTV) was extended for 0–5 mm from the GTV. The internal target volume (ITV) was determined from slow-rotation CT images and from respiratory-driven tumor motion on the simulator. The planning target volume (PTV) was extended for 5 mm from the ITV. The SBRT plan was created with a 3D radiotherapy planning system (CAD Plan/Eclipse, Varian Medical Systems). SBRT was delivered with a linear accelerator (Clinac

Table 1. Patients' characteristics and irradiation dose characteristics

	Number of lesions (%)	
Gender	Female	8 (21%)
	Male	30 (79%)
Age (years)	<69	3 (8%)
	70–79	19 (50%)
	80–89	16 (42%)
Performance status	0–1	32 (84%)
	2–3	6 (16%)
Histology	SCC	9 (24%)
	Adeno	15 (39%)
	NSCLC-NOS	2 (5%)
	Undiagnosed	12 (32%)
Operability	Operable	17 (45%)
	Inoperable	21 (55%)
Tumor diameter (cm)	Median 2.3 (0.9–4.2)	
T stage	T1a	11 (29%)
	T1b	15 (39%)
	T2a	12 (32%)
Tumor location	Upper lobe	24 (63%)
	Middle or lower lobe	14 (37%)
GGN type	Solid GGN	36 (95%)
	Part solid - pure GGN	2 (5%)
BED ₁₀	≥100	17 (45%)
	<100	21 (55%)
Single dose	≥10 Gy	21 (55%)
	<10 Gy	17 (45%)

SCC = squamous cell carcinoma, Adeno = adenocarcinoma, NSCLC-NOS = non-small cell lung cancer not otherwise specified, GGN = ground glass nodule, BED₁₀ = biological effective dose calculated using $\alpha/\beta = 10$.

23EX, Varian Medical Systems) using 6-MV X-ray beams with five to seven non-coplanar multistatic ports and/or multidynamic arcs.

Before June 2009, the dose calculation algorithm was based on the pencil beam method with heterogeneity correction (modified Batho power law). Sixty Gy in 15 fractions, 60 Gy in 8 fractions, or 48 Gy in 4 fractions was prescribed to the isocenter. After June 2009, the dose calculation algorithm was changed to the analytical anisotropic algorithm. Fifty Gy in 8 fractions or 40 Gy in 4 fractions was delivered to cover 95% of the PTV (D95).

Table 2. Treatment procedure

Immobilization:	Vacuum cushions (Vac-loc, Med-tek) with or without an abdominal pressure belt
Computed tomography:	Slow-rotation CT scanning (slice thickness, 2.5 mm; 4 s/slice)
ITV definition:	Slow-rotation CT and lung tumor motion on the simulator (Varian Ximatron)
SBRT planning	Varian CADPlan or Eclipse
Prescription:	
Isocenter prescription	60 Gy/15 fr, 60 Gy/8 fr and 48 Gy/4 fr
D95 prescription	50 Gy/8 fr and 40 Gy/4 fr
Algorithm:	PBC with Modified Batho Power Law correction or AAA
Irradiation machine:	Varian Clinac 23EX
Beam arrangement:	Multistatic beams, typically four non-coplanar and three coplanar static beams using 6-MVX beams

ITV = internal target volume, SBRT = stereotactic body radiation therapy, D95 = 95% of the PTV.

This study was approved by the Ethical Committee of our institution, and written informed consent was obtained from all patients.

Follow-up after SBRT

Patients consulted a radiation oncologist 4–6 weeks after treatment. Around the same time, CT scanning was performed. Thereafter, the patients had follow-up examinations every 3–6 months for 2 years following treatment, then every 6 months.

FDG-PET/CT methods

The median time from FDG-PET/CT to the first day of SBRT was 30 days (range, 3–58 days). After a 4-h fast, patients were injected with 3.7 MBq FDG/kg. After 60 min, a whole body scan was performed using a PET/CT scanner (Biograph Duo LSO or Biograph 40 Truepoint; Siemens Medical Solution, Erlangen Germany).

Metabolic parameters

One radiologist analyzed pretreatment FDG-PET images for 38 patients and measured SUV_{max} , MTV_2 , MTV_4 , MTV_6 , $TLG_{40\%}$, $TLG_{50\%}$ and $TLG_{60\%}$. MTV_X was defined as the volume for which the SUV was over or equal to X [5]. The volume of interest (VOI) sufficiently enclosed the SUV area, and the volume greater or equal to $SUV = X$ was automatically measured (Fig. 1A). $TLG_{X\%}$ was defined as $MTV_{X\%} \times SUV_{mean}$ [6]. $MTV_{X\%}$ was defined as the volume over or equal to X% of SUV_{max} . For example, when SUV_{max} was 8, $MTV_{40\%}$ was the volume over or equal to the SUV of 3.2. When there was confusion regarding the $MTV_{X\%}$ area and lung

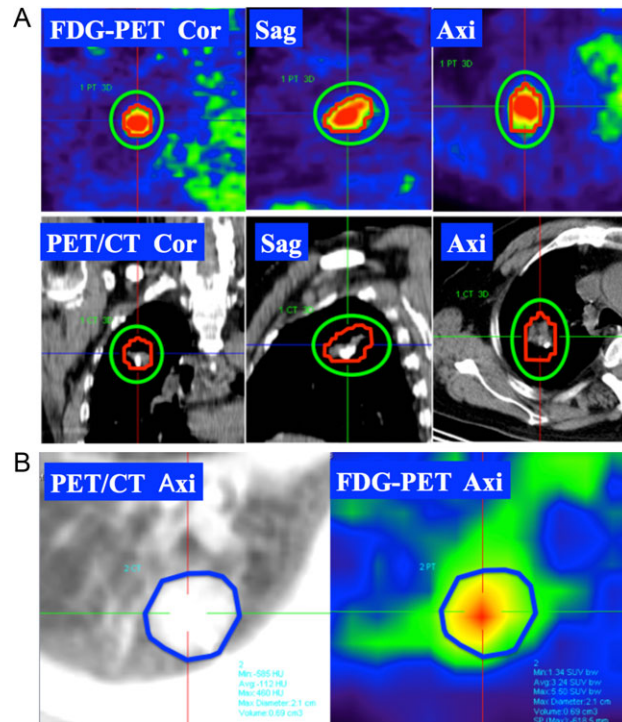


Fig. 1. Measurement of metabolic tumor volume (MTV) and mean maximum standardized uptake value (SUV_{mean}). (A) We made the volume of interest (VOI) to sufficiently surround the fluorodeoxyglucose (FDG) uptake area (green line). The volume of over or equal to the FDG value X was automatically measured (red line). (B) SUV_{mean} was defined as the average of the SUV in the outline of the tumor at the level of the greatest tumor dimensions at the pulmonary window of a positron emission tomography – computed tomography (PET/CT) axial image.

background, we used the tumor volume as $MTV_{X\%}$. We contoured an outline of the tumor on the slice showing the maximum tumor dimension at the pulmonary window of PET/CT, and we defined MTV_{mean} as the average of SUV in the outline (Fig. 1B).

Statistical analysis

Statistical analysis was performed by using JMP® pro v.11.0.0 (SAS Institute). OS and LC rates were calculated from the first day of SBRT to the day of an event. Prognostic factors for OS and LC rates, including age, gender, tumor diameter, biological effective dose (BED_{10}), single dose, SUV_{max} , MTV_2 , MTV_4 , MTV_6 , $TLG_{40\%}$, $TLG_{50\%}$ and $TLG_{60\%}$, were investigated by Cox's proportional hazards model for univariate analyses. Multivariate analysis was not performed because of the small number of patients. BED_{10} was calculated using the following formula: $BED_{10} = nd(1 + d/\alpha/\beta)$, where n is the number of fractions, d is a single dose, and α/β is 10 Gy. OS and LC rates were calculated using the Kaplan–Meier method. We made receiver operating characteristics curves (ROC curves) for PET parameters for OS and LC rates. Regarding OS, the 3-year OS rate

was 56.4%, and the median follow-up period in patients who survived was ~36 months. Therefore, we set the cut-off value to 36 months, and we considered survival for >36 months to be 'true' and survival for <36 months to be 'false'. Absence of local recurrence was 'true' and presence of local recurrence was 'false' for LC. We compared them with the volumes of area under the curve (AUC) by using χ^2 test. $P < 0.05$ was defined as significant in all tests. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.0.

RESULTS

Treatment outcomes

The median follow-up periods were 30 months (range, 5.6–82 months) in all patients and 37.7 months (range, 17.4–82 months) in patients who survived.

The 3-year OS rate was 56.4% [95% confidence interval (CI): 39.4–72.1] and the 5-year OS rate was 36.8% (95% CI: 18.3–60.2). Nine patients died of NSCLC, and nine patients died of other causes. Local recurrence was seen in seven patients, and nine patients had distant organ metastases. The 3-year LC rate was 70.5% (95% CI: 46.9–86.6) and the 5-year LC rate was 70.5% (95% CI: 46.9–86.6).

Grade 2 or 3 radiation pneumonitis occurred in seven patients, and Grade 5 radiation pneumonitis occurred in one patient.

FDG-PET/CT parameters

The median SUV_{max} was 6.32 (range: 0.65–23.6). The median values of MTV_2 , MTV_4 and MTV_6 were 5.75 cm³ (range: 0–82.1 cm³), 2.03 cm³ (range: 0–31.5 cm³) and 0.04 cm³ (range: 0–21.7 cm³), respectively. The median values of $TLG_{40\%}$, $TLG_{50\%}$ and

$TLG_{60\%}$ were 12.7 (range: 0.016–205), 8.2 (range: 0.016–111) and 5.17 (range: 0.016–78.7), respectively.

Univariate analyses

In univariate analyses, tumor diameter [$P = 0.019$, hazard ratio (HR): 1.99, 95% CI: 1.12–3.58], single dose ≥ 10 Gy (≥ 10 Gy vs <10 Gy; $P = 0.017$, HR: 0.35, 95% CI: 0.11–0.81), MTV_2 ($P = 0.030$, HR: 1.03, 95% CI: 1.00–1.05) and MTV_4 ($P = 0.047$, HR: 1.06, 95% CI: 1.00–1.11) were significant predictors of OS, and tumor diameter ($P < 0.001$, HR: 11.1, 95% CI: 2.98–69.2), single dose ≥ 10 Gy ($P = 0.007$, HR: 0.10, 95% CI: 0.01–0.56), SUV_{max} ($P = 0.035$, HR: 1.18, 95% CI: 1.01–1.37), MTV_2 ($P < 0.001$, HR: 1.10, 95% CI: 1.04–1.18), MTV_4 ($P = 0.003$, HR: 1.15, 95% CI: 1.05–1.26), MTV_6 ($P = 0.017$, HR: 1.17, 95% CI: 1.04–1.32), $TLG_{40\%}$ ($P < 0.001$, HR: 1.03, 95% CI: 1.02–1.06), $TLG_{50\%}$ ($P = 0.001$, HR: 1.04, 95% CI: 1.02–1.05) and $TLG_{60\%}$ ($P = 0.003$, HR: 1.06, 95% CI: 1.02–1.10) were significant predictors of LC. SUV_{max} was not a significant predictor of OS (Table 3).

ROC curves

The AUC values of SUV_{max} , MTV_2 , MTV_4 , MTV_6 , $TLG_{40\%}$, $TLG_{50\%}$ and $TLG_{60\%}$ for survival were 0.542, 0.630, 0.601, 0.564, 0.625, 0.619 and 0.616, respectively. The largest AUC for survival was MTV_2 ; the AUC of MTV_2 was significantly different from the AUC of SUV_{max} ($P = 0.0319$, Fig. 2A). Of the patients who were followed up for <36 months, three patients (~7.9% of all patients) were lost to follow-up. On the other hand, AUC values of SUV_{max} , MTV_2 , MTV_4 , MTV_6 , $TLG_{40\%}$, $TLG_{50\%}$ and $TLG_{60\%}$ for LC were 0.590, 0.645, 0.668, 0.608, 0.719, 0.701 and 0.687, respectively. The largest AUC

Table 3. Univariate analyses for OS and LC

Variables	UVA for OS		UVA for LC	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.07 (0.99–1.17)	0.072	1.01 (0.92–1.14)	0.789
Gender	2.66 (0.75–16.8)	0.141	0.86 (0.18–6.03)	0.859
Tumor diameter (cm)	1.99 (1.12–3.58)	0.019*	11.1 (2.98–69.2)	<0.001*
BED ₁₀ ≥ 100 or not	0.78 (0.29–2.03)	0.606	0.48 (0.07–2.25)	0.365
Single dose ≥ 10 Gy or not	0.35 (0.11–0.81)	0.017*	0.10 (0.01–0.56)	0.007*
SUV_{max}	1.07 (0.99–1.14)	0.086	1.18 (1.01–1.37)	0.035*
MTV_2	1.03 (1.00–1.05)	0.030*	1.10 (1.04–1.18)	<0.001*
MTV_4	1.06 (1.00–1.11)	0.047*	1.15 (1.05–1.26)	0.003*
MTV_6	1.07 (0.97–1.15)	0.155	1.17 (1.04–1.32)	0.017*
$TLG_{40\%}$	1.01 (0.99–1.02)	0.056	1.03 (1.02–1.06)	<0.001*
$TLG_{50\%}$	1.02 (0.99–1.03)	0.057	1.04 (1.02–1.08)	0.001*
$TLG_{60\%}$	1.02 (0.99–1.04)	0.070	1.06 (1.02–1.10)	0.003*

UVA = univariate analyses, OS = overall survival, LC = local control, HR = hazard ratio, CI = confidence interval, BED₁₀ = biological effective dose calculated using $\alpha/\beta = 10$.

*Including conventional radiation therapy.

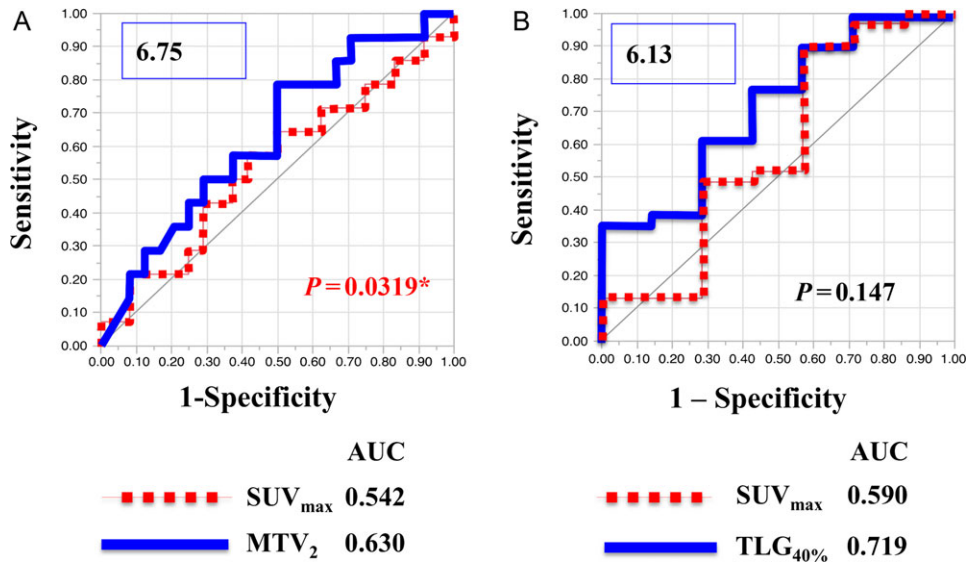


Fig. 2. Receiver operating characteristics curves (ROC curves) for survival and local recurrence. (A) The ROC curve for MTV₂ for survival indicated that the cut-off value was 6.75. The AUC for MTV₂ was 0.630 and was compared with the AUC for SUV_{max} using the χ^2 test. (B) The ROC curve for TLG_{40%} for local control indicated that the cut-off value was 6.13. The AUC for TLG_{40%} was 0.719 and was compared with the AUC for SUV_{max} by using the χ^2 test.

for LC was TLG_{40%}; the AUC for LC of TLG_{40%} was not significantly different from the AUC for SUV_{max} ($P = 0.147$, Fig. 2B).

DISCUSSION

SBRT is a safe and effective treatment method for inoperable patients with early-stage NSCLC [1]. The effectiveness of SBRT has also been shown in operable patients, and SBRT has become an option for treatment of patients with early-stage NSCLC. If we can predict that SBRT will be effective for a patient before treatment, we can strongly recommend SBRT. It will be possible to give patients tailor-made medicine if a predictive factor is established. We previously reported some possible prognostic factors, including BED₁₀, metastatic tumor, broad attachment to the pleura, and minimum PTV dose [8–10]. The results of the present study suggest that MTV and TLG also have potential as prognostic factors for LC and OS after SBRT.

Several studies have shown results of SBRT for early-stage lung cancer. LC rates were 86.0–98.2% and 3-year OS rates were 42.7–83% in past studies [1,2,11,12]. In our study, the LC rate was 81.6% (31/38) and the 3-year OS rate was 56.4%. The 3-year OS rate in our study is consistent with the results of most past studies, but is worse than the result reported by Nagata *et al.* [11]. The LC rate in our study was relatively poor compared with the results of past studies. The possible reason for the worse LC rate might be that half of the patients were treated using a BED₁₀ of <100 due to bad performance status and bad pulmonary function. Despite the fact that the median age of patients enrolled in our study was higher than the median ages of patients in other studies, the 3-year OS rate in our study was comparable with the rates in other studies.

In this study, BED₁₀ was not a significant predictor of OS and LC rates in Cox’s proportional hazards model. On the other hand, a single dose ≥ 10 Gy was a significant predictor of OS and LC rates.

Table 4. Usefulness of pre-SBRT FDG-PET/CT

Authors	N	TNM	Median follow-up (months)	Possibility of SUV _{max} as a prognostic factor
Hoopse <i>et al.</i> [13]	32	T1–2N0M0	42.5	LCR No OS No
Hamamoto <i>et al.</i> [14]	26	T1–2N0M0	21	LCR Yes
Takeda <i>et al.</i> [15]	97	T1–4N0M0	18	LCR Yes
Burdick <i>et al.</i> [16]	72	T1–2N0M0	16.7	LCR No OS No
Nair <i>et al.</i> [17]	163*	T1–2N0M0	16	LRFS No DMFS Yes OS No

*Including SBRT and conventional radiation therapy.

N = number of patients, SBRT = stereotactic body radiation therapy, FDG-PET/CT = fluorodeoxyglucose positron emission tomography / computer tomography, SUV_{max} = maximum standardized uptake value, LCR = local control rate, OS = overall survival, LRFS = local recurrence-free survival, DMFS = distant metastasis-free survival.

Our institution has recently been prescribing 40 Gy in four fractions to cover 95% of the PTV (D95) using the analytical anisotropic algorithm. A BED₁₀ is calculated to be 80 when a single dose of 10 Gy is used. However, it is difficult to compare a BED₁₀ of isocenter prescription with that of D95 prescription. In this study, 40 Gy in four fractions using D95 prescription was considered to be a BED₁₀ of <100. This might be a reason why BED₁₀ was not a significant predictor in this study.

SUV_{max} was not a significant predictor of OS in univariate analyses in our study. It is controversial whether SUV_{max} is useful as a prognostic factor. Hamamoto *et al.*, Takeda *et al.* and Nair *et al.* reported that SUV_{max} had potential as a prognostic factor, but Hoopse *et al.* and Burdick *et al.* reported that SUV_{max} did not have potential as a prognostic factor [13–17] (Table 4). There are several pitfalls to be aware of concerning the value of SUV_{max}. For example, when the tumor is small, it is known that the value of SUV_{max} is underestimated (a volume effect), and when the tumor is located in a large physiological movement region, the value of SUV_{max} is underestimated (due to motion blur). Stage I lung cancer tumors are small and have respiratory movement, and it is therefore possible that the value of SUV_{max} can be underestimated. Therefore, it is not clear whether SUV_{max} is a prognostic factor in patients with Stage I NSCLC treated with SBRT.

The results of univariate analyses indicated that MTV₂ and MTV₄ were prognostic factors for OS, but that SUV_{max} was not. The AUC value of MTV₂ was significantly larger than that of SUV_{max}. However, SUV_{max} was not a significant prognostic factor in univariate analysis, and the largest AUC value for OS was for MTV₂. We think MTV₂ is a better prognostic factor than SUV_{max} for OS. Regarding the LC rate, SUV_{max}, MTV₂, MTV₄, MTV₆, TLG_{40%}, TLG_{50%} and TLG_{60%} were prognostic factors in univariate analyses. There was no significant difference between the AUC value of TLG_{40%} and that of SUV_{max}. However, the AUC value of TLG_{40%} was larger than that of SUV_{max}, and it is therefore possible that TLG_{40%} is a better prognostic factor than SUV_{max} for LC. In this study, local recurrence was observed in only seven patients. In the future, we will analyze data for a larger number of patients. The results of our study suggest that MTV₂ was a prognostic factor for OS, and a significantly better factor than SUV_{max}. However, when the value of X goes down, it is possible that MTV_x and TLG_x correlate strongly with tumor volume. The reason that PET parameters of small X are better prognostic factors may be simply that they reflect tumor volume.

In order to calculate TLG_x, SUV_{mean} must be calculated. The definition of SUV_{mean} is very difficult. In this study, we defined the region of interest for SUV_{mean} on the slice showing the maximum tumor dimension at the pulmonary window of PET/CT. However, when the tumor is located at the lower lobe of the lung, there is sometimes deviation in PET and CT fusion images. Therefore, it is questionable whether it is the true SUV average of the tumor. In the future, it will be necessary to define SUV_{mean}, and we propose to repeat this study using 4D PET, with the addition of respiratory motion.

MTV_x and TLG_x are parameters reflecting both tumor volume and FDG accumulation. In this study, MTV₂ was a significant factor for OS in Cox's hazards model analysis, and MTV₂ was shown by AUC comparison to be a significantly better prognostic factor than SUV_{max} for OS. FDG-PET/CT is very useful for detecting distant metastasis and lymph node metastasis, but it is inadequate for diagnosing and predicting prognosis from SUV_{max} only. It is necessary to examine other parameters in the future. Our results suggested that MTV₂ is a better prognostic factor for OS of patients with Stage I lung cancer treated with SBRT. In order to provide patients

with tailor-made medicine, further study of prognostic factors is necessary.

CONCLUSION

In conclusion, MTV₂ on pretreatment FDG-PET/CT is a significant predictor of OS. MTV₂ is a better prognostic factor than other FDG-PET/CT parameters, including SUV_{max} for OS. By using MTV₂ as well as other predictors, personalized medicine might become a reality, but further study is needed.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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