



Metabolic volume parameters based on different thresholds with baseline ¹⁸F-FDG PET/CT as prognostic factors for survival in stage III non-small cell lung cancer

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Background: Concurrent chemo-radiotherapy is recommended as the standard treatment of stage III non-small-cell lung cancer (NSCLC) patients. However, the 5-year survival has not significantly improved during the past decade. Therefore, it is essential to find prognostic factors for specific cohort of patients. Studies have indicated that the intratumoral heterogeneity can be described by the variability in the voxel intensity of Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) within the tumor volume (TV). Hence, we presumed that certain thresholds of metabolic volume parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) might serve as prognostic factors of stage III NSCLC patients.

Methods: A total of 78 cases with stage III NSCLC were confirmed by histology or cytology and treated with concurrent chemo-radiotherapy. We computed MTV on the basis of different thresholds of standardized uptake value (SUV). TLG was calculated as the MTV multiplied by the SUV_{mean} . The prognostic values of the PET parameters and clinical variables were assessed with Cox proportional hazards regression analysis of the overall survival (OS) and progression-free survival (PFS) for both univariate and multivariate analyses.

Results: The median follow-up time for all patients was 24.5 months (range 12–39 months). In the univariate analysis, $MTV_{50\%}$, $MTV_{60\%}$, $MTV_{70\%}$, $TLG_{50\%}$, $TLG_{60\%}$, ECOG and sex were significant prognostic factors of OS [$P_{(MTV50\%)}=0.013$, $P_{(MTV60\%)}=0.002$, $P_{(MTV70\%)}=0.024$, $P_{(TLG50\%)}=0.013$, $P_{(TLG60\%)}=0.029$, $P_{(ECOG)}=0.011$, $P_{(sex)}=0.008$], while $MTV_{50\%}$, $MTV_{60\%}$, $MTV_{70\%}$, $TLG_{50\%}$, $TLG_{60\%}$, and ECOG were significantly associated with PFS [$P_{(MTV50\%)}=0.004$, $P_{(MTV60\%)}=0.007$, $P_{(MTV70\%)}=0.020$, $P_{(TLG50\%)}=0.006$, $P_{(TLG60\%)}=0.038$, $P_{(ECOG)}=0.005$]. In the multivariate analysis, $TLG_{50\%}$ was significantly associated with OS (HR =0.423, $P=0.023$), and also significant prognostic factor of PFS [HR =0.457, $P_{(TLG50\%)}=0.029$]. $MTV_{60\%}$ was significantly associated with PFS (HR =0.402, $P_{(MTV60\%)}=0.042$). These PET/CT parameters were separately analyzed and were adjusted for age, sex, stage, histology, ECOG, and location.

Conclusions: Volume-based PET pretreatment parameters have prognostic value in nonsurgical stage III NSCLC. A higher $MTV_{60\%}$ predicts a worse PFS. $TLG_{50\%}$ is negatively correlated with both OS and PFS. These would be helpful to identify proper cohorts for individualized therapeutic schedules.

Keywords: $MTV_{60\%}$; $TLG_{50\%}$; prognosis; non-small-cell lung cancer (NSCLC)

Submitted Feb 02, 2017. Accepted for publication Jun 18, 2017.

doi: 10.21037/tcr.2017.06.52

View this article at: <http://dx.doi.org/10.21037/tcr.2017.06.52>

Introduction

Stage III non-small-cell lung cancer (NSCLC), comprising 25% to 30% of the total cases of NSCLC, manifests in a range of heterogeneous patients, from those with potentially operable lesions to those with inoperable advanced lesions (1,2). There is a marked inhomogeneity in outcomes in patients with stage III NSCLC presenting with the same performance status (3,4). At present, concurrent chemo-radiotherapy is recommended as the standard treatment for nonsurgical stage III NSCLC patients. Disappointingly, the 5-year survival has not significantly improved during the past decade (5,6). To improve the outcomes of patients, better and more detailed individualized treatments must be developed, and doing so depends on the identification of a more reliable prognostic factor. Therefore, it is essential to find prognostic factors for specific cohort of patients.

Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is widely used for diagnosis and staging in lung cancer, and volume-based metabolic parameters, such as the metabolic tumor volume (MTV) and total lesion glycolysis (TLG), have been investigated for their prognostic value in NSCLC. However, there is still no consensus in the literature on the prognostic value of metabolic parameters (7-11).

Malignant tumors are notably heterogeneous and composed of different cell subgroups with different characteristics of perfusion, hypoxia, cell density, and proliferation (12-14). Tumor recurrence or metastasis depends primarily on these specific cell subgroups (15-18). Studies have indicated that the intratumoral heterogeneity can be described by the variability in the voxel intensity of FDG PET within the tumor volume (TV) (19,20). Consequently, we predicted a ladder-like distribution of the tumor metabolism on which different levels may represent diverse biological characteristics. Hence, we presumed that different thresholds of the MTV or TLG might serve as prognostic factors.

Our study focused on the prognostic value of the MTV with different SUV thresholds of FDG PET/CT. Our intention was to refine the prognostic analysis of the volume-based metabolic parameters of FDG PET/CT in patients with nonsurgical stage III NSCLC.

Methods

Patients

A total of 78 cases of stage III NSCLC (AJCC stage)

were confirmed by histology or cytology and treated with concurrent chemo-radiotherapy in the Radiotherapy Department in Shandong Cancer Hospital between January 2009 and December 2012. All cases had undergone FDG PET/CT pretreatment and subsequently concurrent chemo-radiotherapy. We conducted the study under the review and approval of the Institutional Review Committee of the Cancer Hospital of Shandong Province, and all the patients signed informed consent (ID of Ethics Approval: 201208020). The median interval from PET/CT to chemo-radiotherapy was 11 days (range 4–21 days). Before treatment, the patients were examined for staging, which included bronchoscopy, transthoracic biopsy, CT or MR of the brain, and contrast-enhanced CT of the chest and abdomen. The exclusion criteria were previous thoracic surgery, chemotherapy or radiotherapy or diabetes. We recorded the clinical variables, such as sex, age, stage, histology, ECOG performance status, EGFR mutations, tumor location. NSCLC could be divided into central and peripheral tumors by its location. Central tumors were defined as those within 2 cm of the proximal bronchial tree or immediately adjacent to mediastinal/pericardial pleura; Tumors that did not meet this criterion were defined as peripheral-type tumors (21). The patients' characteristics are summarized in *Table 1*.

After the completion of the treatment, all patients were followed up every three months. A physical examination and contrast-enhanced CT of the chest and abdomen were included in the follow-up evaluation. All the patients were followed up until December 31st 2015 or their date of death, and the median follow-up time was 24.5 months (range 12–39 months). Each of patients was scored for the endpoints of overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the day of the treatment beginning to the day of the last follow-up or death, and PFS was calculated from the day of the treatment beginning to the day of local or distant disease progression. The estimated median PFS was 11.0 months (range 3–23 months). The estimated median OS was 19.0 months (range 10–38 months).

18F-FDG PET/CT imaging/analysis

All patients rested and fasted for more than 6 h before the PET/CT (Discovery LS PET/CT system, GE Healthcare) examination. Briefly, the serum glucose was determined to ensure controlled levels below 6.6 mmol/L. Patients waited 55±5 min (range, 45–60 min; median, 55 min) after

Table 1 Summary of patients' characteristics

Parameters	No. of patients
Sex	
Male	47
Female	31
Age (years)	
<60	36
≥60	42
ECOG performance status	
0–1	40
2–3	38
AJCC stage	
IIla	35
IIlb	43
T stage (1/2/3/4)	
T1/2	25
T3/4	53
N stage (0/1/2/3)	
N0/1	11
N2/3	67
Histological nature	
Adenocarcinoma	34
Squamous cell carcinoma	33
Unspecified NSCLC	11
Location	
Central	37
Peripheral	41
Mutation	
EGFR(19/21) +	17
EGFR(19/21) –	61

AJCC, American Joint Committee on Cancer; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group.

the intravenous infusion of 10 mCi of ¹⁸F-FDG, and then PET imaging was performed from the head to the upper thighs. Both the PET and the CT images were taken during normal breathing. The PET images were reconstructed by using the ordered subset expectation maximization (OSEM)

algorithm with the CT-derived attenuation correction. The PET images, attenuation-corrected CT images, and fusion PET/CT images were displayed as coronal, axial and sagittal planes. We viewed and analyzed these images on a Xeleris workstation (GE Healthcare).

The parameters of the PET/CT images, which included the MTV, TLG, SUV_{mean}, and SUV_{max} of the primary tumor, were assessed and recorded by two experienced nuclear medicine physicians. MTV represents the TV with an SUV equal to or greater than a specified threshold. We computed MTV_{2.5} on the basis of an absolute SUV threshold of 2.5. We also evaluated MTV values on the basis of relative thresholds, i.e., MTV_{40%}, MTV_{50%}, MTV_{60%}, MTV_{70%}, MTV_{80%}, and MTV_{90%}, which were defined as volumes with an SUV greater than 40%, 50%, 60%, 70%, 80%, and 90% of SUV_{max}, respectively. The MTV was automatically delineated on the PET/CT images with the specified SUV, such as a contour line, and then calculated with the software. The SUV_{max} and SUV_{mean} for each MTV were also calculated automatically. TLG_{50%} was calculated as MTV_{50%} multiplied by the SUV_{mean}, and TLG_{60%} was calculated in a similar manner. To obtain the CT based tumor volume (CTV), we also delineated the primary tumor and calculated the volume on CT scan, using the lung window setting (window width, 1,000 HU; window center, –700 HU) as our previous research did (22).

The area under the curve of cumulative SUV-volume histograms (AUC-CSH) was used to evaluate intratumoral metabolic heterogeneity, and the CSH was obtained by plotting the percent volume of a tumor with a SUV above a certain threshold against that threshold, which was varied from 0 to 100 % of SUV_{max} (23). In order to calculate the percent volume of the tumor, the threshold SUV intensity value exceeding 3.0 was used as the region of interest (ROI) (24). AUC-CSH was extracted from the ROI. Image analysis was performed using an in-house MATLAB code (Mathworks Inc., Natick, USA). *Figure 1* shows the typical examples of homogeneity (A) and heterogeneity (C) FDG uptake in two patients, whose AUC were 0.74 (B) and 0.37 (D) respectively.

Chemo-radiotherapy

All the patients underwent radiotherapy, which was performed with megavoltage equipment (6 MV) with an intensity-modulated radiotherapy (IMRT)/three-dimensional conformal radiotherapy (3D-CRT) technique.

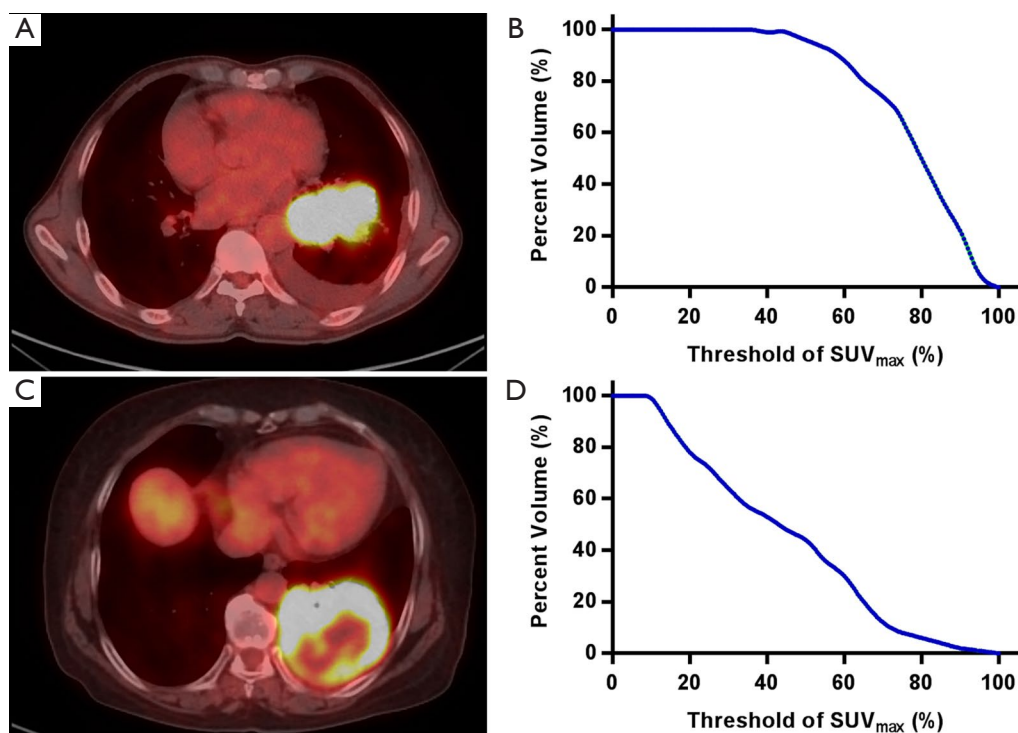


Figure 1 Representative FDG PET/CT images of two patients shown with homogeneity (A,B) and heterogeneity (C,D), and AUC were 0.74 and 0.37 respectively. Patient's OS with lower AUC was 15 months, the other patient's OS was 19 months. FDG, Fluorine 18 fluorodeoxyglucose; PET, positron emission tomography; OS, overall survival; AUC, area under the curve.

Thoracic radiotherapy was implemented as conventionally fractionated radiotherapy with 5×2 Gy per week to a total dose of at least 60 Gy. The radiotherapy plan was based on a planning CT image. The gross tumor volume (GTV) comprised the primary tumor and included the lymph nodes, and the planning target volume (PTV) comprised the GTV with an edge expansion of 10–15 mm. All patients underwent two cycles of concurrent chemo-radiotherapy with cisplatin-based doublet chemotherapy, with or without adjuvant chemotherapy.

Statistical analysis

We analyzed the data by using SPSS version 22.0 (SPSS, Inc.; IBM Co.). The Cox proportional hazards model was used to estimate variables for the univariate and multivariate analyses in our study. These variables included the PET/CT parameters and some clinical variables, such as sex, age, tumor location, ECOG, stage and histology. For the intent of statistical analyses, clinical variables were divided into two or three categories; For the age of patients, 60 years was selected as the cutoff for classification

routinely; SUV_{max} , AUC-CSH, CTV, $MTV_{2.5}$, $MTV_{40\%}$, $MTV_{50\%}$, $MTV_{60\%}$, $MTV_{70\%}$, $MTV_{80\%}$, $MTV_{90\%}$, $TLG_{50\%}$, $TLG_{60\%}$ were considered as binary variables by dividing patients into pairs of subgroups on the basis of the median values of the above parameters. The differences in the estimated factors among the subgroups were evaluated using the log-rank test.

Also, we evaluated correlation coefficients of the independent variables. We used Spearman rank correlation for non-continuous variables, and Pearson correlation for continuous variables. The correlation coefficients between the PET parameters and the CTVs ($MTV_{2.5}$ vs. CTV, $MTV_{40\%}$ vs. CTV, $MTV_{50\%}$ vs. CTV, $TLG_{50\%}$ vs. CTV, $TLG_{60\%}$ vs. CTV) were higher than 0.700 (0.985, 0.883, 0.802, 0.793, 0.755 respectively), and the correlation coefficients between the PET parameters ($MTV_{2.5}$ vs. $MTV_{40\%}$, $MTV_{40\%}$ vs. $MTV_{50\%}$, $MTV_{70\%}$ vs. $MTV_{80\%}$, $MTV_{50\%}$ vs. $TLG_{50\%}$, $TLG_{50\%}$ vs. $TLG_{60\%}$) were also very high (0.856, 0.922, 0.710, 0.781, 0.922, respectively), therefore, to avoid multicollinearity, each multiple variable regression model included one PET parameter or CTV and other clinical variables.

Differences were considered to be significant when the two-tailed P value was less than 0.05.

Results

PET/CT parameters of primary tumor

In order to analyze the prognostic value of metabolic volume parameters, we assessed and recorded each patient's PET/CT metrics. The median SUV_{max} of the primary tumor was 13.0 (range 3.8–22.0), and the median values of $TLG_{50\%}$ and $TLG_{60\%}$ were 111.5 (range 8.6–547.7) and 74.1 (range 5.4–479.7), respectively. The median MTV values in mL were $MTV_{2.5}$ of 52.1, $MTV_{40\%}$ of 29.6, $MTV_{50\%}$ of 15.8, $MTV_{60\%}$ of 8.7, $MTV_{70\%}$ of 4.0, $MTV_{80\%}$ of 1.5, and $MTV_{90\%}$ of 0.3.

PET/CT parameters and survival

To evaluate the prognostic impacts of patients' characteristics and the PET/CT parameters, we used the univariate analyses for OS and PFS with Cox Proportional Hazards Model. In the univariate analysis, $MTV_{50\%}$, $MTV_{60\%}$, $MTV_{70\%}$, $TLG_{50\%}$, $TLG_{60\%}$ and sex, ECOG were significant prognostic factors of OS [HR =0.489, $P_{(MTV50\%)}=0.013$; HR =0.414, $P_{(MTV60\%)}=0.002$; HR =0.534, $P_{(MTV70\%)}=0.024$; HR=0.513, $P_{(TLG50\%)}=0.013$; HR =0.549, $P_{(TLG60\%)}=0.029$; HR=0.454, $P_{(sex)}=0.008$, HR=0.500, $P_{(ECOG)}=0.011$], while $MTV_{50\%}$, $MTV_{60\%}$, $MTV_{70\%}$, $TLG_{50\%}$, $TLG_{60\%}$ and ECOG were significantly associated with PFS [HR =0.477, $P_{(MTV50\%)}=0.004$; HR=0.500, $P_{(MTV60\%)}=0.007$; HR=0.554, $P_{(MTV70\%)}=0.020$; HR =0.502, $P_{(TLG50\%)}=0.006$; HR =0.596, $P_{(TLG60\%)}=0.038$; HR =0.496, $P_{(ECOG)}=0.005$]. Detailed results of this analysis are shown in Table 2. The HRs of variables, such as age ≥ 60 years, male, IIIb, ECOG 2–3, T_3/T_4 , N_2/N_3 , non-adenocarcinoma, and peripheral type were all 1.0.

In the multivariate analysis, $TLG_{50\%}$ was significantly associated with OS (HR =0.423, $P=0.023$), and also significant prognostic factor of PFS [HR =0.457, $P_{(TLG50\%)}=0.029$]. $MTV_{60\%}$ was significantly associated with PFS (HR =0.402, $P_{(MTV60\%)}=0.042$). SUV_{max} was not an independent prognostic factor for nonsurgical stage III NSCLC in terms of the OS or PFS (HR =0.885, $P=0.717$; HR =0.928 $P=0.809$). These PET/CT parameters were separately analyzed and were adjusted for age, sex, stage, histology, ECOG, and location. Figure 2 shows a typical example of two patients with stage III NSCLC. They had

similar values of $MTV_{50\%}$ (34.6 vs. 37.4 mL) but different values of $MTV_{60\%}$ (10.4 vs. 21.2 mL). The patient with a lower $MTV_{60\%}$ had a longer PFS (13 vs. 7 months). Detailed results of this analysis are shown in Table 3.

Prognostic stratification by $MTV_{60\%}$ and $TLG_{50\%}$

To validate the prognostic roles of $MTV_{60\%}$ and $TLG_{50\%}$, we divided the patients into two pairs of subgroups on the basis of the median values of $MTV_{60\%}$ and $TLG_{50\%}$. Figure 3A shows the PFS for patients with $MTV_{60\%}$ above or below the median. The PFS difference between the groups was significant, with a P value of 0.003, and patients with a higher $MTV_{60\%}$ demonstrated a worse survival. Patients with a $MTV_{60\%}$ more than 8.7 mL demonstrated worse PFS (median 9 months; 95 % CI: 6.986 to 11.014) compared to less than 8.7 mL (median 12 months; 95 % CI: 9.990 to 14.010). Figure 3B,C show the OS and PFS for patients with $TLG_{50\%}$ above or below the median respectively. Improved OS and PFS were significantly associated with a lower $TLG_{50\%}$ ($P=0.035$, $P=0.003$). $TLG_{50\%}$ more than 111.5 (median 19 months; 95% CI: 16.835 to 21.165) demonstrated worse OS compared to less than 111.5 (median 23 months; 95% CI: 21.820 to 24.180), and $TLG_{50\%}$ more than 111.5 (median 9 months; 95% CI: 6.961 to 11.039) demonstrated worse PFS compared to less than 111.5 (median 12 months; 95% CI: 10.381 to 13.619).

Discussion

A prognostic assessment of pretreatment is important for improving survival because it enables patients to be stratified into optimal therapeutic regimens. We analyzed the prognostic roles of SUV_{max} and different thresholds of MTV and TLG in addition to the clinical variables of nonsurgical stage III NSCLC. Our results indicated that $MTV_{60\%}$ was significantly associated with the PFS in nonsurgical stage III NSCLC. $TLG_{50\%}$ was significantly correlated with OS and PFS in the cohort. However, our results suggested that SUV_{max} was not a reliable prognostic factor for survival in nonsurgical stage III NSCLC.

Notably, we found that $MTV_{60\%}$ presented a significant correlation with the PFS (HR =0.402, $P=0.042$). In previous studies, MTV has been identified as a prognostic factor for survival but with various defined criteria (9,10,25,26). Bazan *et al.* demonstrated that pretreatment MTV was highly prognostic for OS and local-regional control (LC) in a

Table 2 Univariate Cox regression analysis

Variables	No. of patients	OS			PFS		
		HR	95% CI	P	HR	95% CI	P
Age							
<60 years	36	0.691	0.413–1.158	0.160	0.830	0.512–1.347	0.451
≥60 years	42						
Sex							
Female	31	0.454	0.253–0.813	0.008 ^a	0.609	0.369–1.007	0.053
Male	47						
AJCC Stage							
IIIa	35	1.056	0.630–1.769	0.837	1.489	0.914–2.424	0.110
IIIb	43						
ECOG							
0–1	40	0.500	0.293–0.855	0.011 ^a	0.496	0.304–0.811	0.005 ^a
2–3	38						
T stage							
T1/2	25	1.069	0.620–1.844	0.810	1.043	0.629–1.729	0.870
T3/4	53						
N stage							
N0/1	11	1.154	0.579–2.299	0.684	1.190	0.617–2.293	0.604
N2/3	67						
CTV (cm³)							
<50.8	39	0.667	0.393–1.131	0.133	0.677	0.413–1.110	0.122
≥50.8	39						
AUC-CSH							
<0.44	39	0.909	0.542–1.254	0.718	1.010	0.621–1.640	0.969
≥0.44	39						
Histology							
Adenocarcinoma	34	1.049	0.625–1.763	0.856	1.164	0.714–1.897	0.543
Non-adenocarcinoma	44						
Location							
Central	37	1.464	0.871–2.463	0.151	0.773	0.478–1.250	0.293
Peripheral	41						
SUV_{max}							
<13.0	39	1.268	0.760–2.117	0.363	0.874	0.538–1.1418	0.585
≥13.0	39						

Table 2 (continued)

Table 2 (continued)

Variables	No. of patients	OS			PFS		
		HR	95% CI	P	HR	95% CI	P
MTV _{2.5}							
<52.1	39	0.649	0.383–1.100	0.108	0.652	0.398–1.067	0.089
≥52.1	39						
MTV _{40%}							
<29.6	39	0.683	0.401–1.162	0.160	0.644	0.394–1.055	0.080
≥29.6	39						
MTV _{50%}							
<15.8	39	0.489	0.278–0.858	0.013 ^a	0.477	0.288–0.789	0.004 ^a
≥15.8	39						
MTV _{60%}							
<8.7	39	0.414	0.237–0.723	0.002 ^a	0.500	0.304–0.824	0.007 ^a
≥8.7	39						
MTV _{70%}							
<4.0	38	0.534	0.309–0.921	0.024 ^a	0.554	0.338–0.910	0.020 ^a
≥4.0	40						
MTV _{80%}							
<1.5	41	0.908	0.542–1.521	0.713	0.829	0.512–1.344	0.448
≥1.5	37						
MTV _{90%}							
<0.3	37	1.021	0.610–1.709	0.938	0.728	0.449–1.183	0.199
≥0.3	41						
TLG _{50%}							
<111.5	39	0.513	0.303–0.868	0.013 ^a	0.502	0.307–0.819	0.006 ^a
≥111.5	39						
TLG _{60%}							
<74.1	39	0.549	0.321–0.939	0.029 ^a	0.596	0.365–0.971	0.038 ^a
≥74.1	39						

^a, statistically significant. AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; CTV, CT-based tumor volume for primary lesion; AUC-CSH, area under the curve of the cumulative SUV-volume histogram; SUV_{max}, maximum standardized uptake value; MTV, metabolic tumor volume; OS, overall survival; PFS, progression-free survival; TLG, total lesion glycolysis.

group of uniformly treated patients with stage III NSCLC in a multi-institutional setting (25). In the investigation, the MTV was defined as all connected voxels with intensity greater than a lesion-specific adaptive threshold of 60% of

the SUV_{peak} within the lesion (25). The SUV_{peak} within the ACRIN 6668 study was defined as the mean SUV within a circular ROI (0.75–1.5 cm in diameter) that encompasses the SUV_{max} (27). Lee *et al.* have reported that a high

Table 3 Multivariate Cox regression analysis

Variables	No. of patients	OS			PFS		
		HR	95% CI	P	HR	95% CI	P
T stage							
T1/2	25	1.176	0.666–2.075	0.577	1.056	0.621–1.795	0.840
T3/4	53						
N stage							
N0/1	11	0.939	0.451–1.958	0.867	0.998	0.490–2.032	0.996
N2/3	67						
CTV (cm ³)							
<50.8	39	0.633	0.357–1.124	0.118	0.672	0.398–1.135	0.137
≥50.8	39						
AUC-CSH							
<0.44	39	0.908	0.539–1.531	0.718	0.967	0.589–1.588	0.896
≥0.44	39						
SUV _{max}							
<13.0	39	0.885	0.457–1.713	0.717	0.928	0.509–1.695	0.809
≥13.0	39						
MTV _{2.5}							
<52.1	39	1.675	0.566–4.963	0.352	1.553	0.619–3.899	0.349
≥52.1	39						
MTV _{40%}							
<29.6	39	1.636	0.694–3.857	0.261	1.297	0.484–3.475	0.605
≥29.6	39						
MTV _{50%}							
<15.8	39	0.669	0.146–3.063	0.605	0.436	0.121–1.577	0.206
≥15.8	39						
MTV _{60%}							
<8.7	39	0.310	0.080–1.194	0.089	0.402	0.167–0.967	0.042 ^a
≥8.7	39						
MTV _{70%}							
<4.0	38	0.714	0.315–1.618	0.419	0.776	0.365–1.649	0.510
≥4.0	40						
MTV _{80%}							
<1.5	41	1.384	0.706–2.712	0.344	1.345	0.731–2.474	0.341
≥1.5	37						

Table 3 (continued)

Table 3 (continued)

Variables	No. of patients	OS			PFS		
		HR	95% CI	P	HR	95% CI	P
MTV _{90%}							
<0.3	37	1.365	0.756–2.466	0.302	1.015	0.571–1.803	0.960
≥0.3	41						
TLG _{50%}							
<111.5	39	0.423	0.202–0.887	0.023 ^a	0.457	0.226–0.923	0.029 ^a
≥111.5	39						
TLG _{60%}							
<74.1	39	0.825	0.332–2.050	0.678	1.891	0.450–7.942	0.384
≥74.1	39						

These PET/CT parameters were separately analyzed and were adjusted for age, sex, stage, histology, ECOG and location. ^a, statistically significant. AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval; CTV, CT-based tumor volume for primary lesion; AUC-CSH, area under the curve of the cumulative SUV-volume histogram; SUV_{max}, maximum standardized uptake value; MTV, metabolic tumor volume; OS, overall survival; PFS, progression-free survival; TLG, total lesion glycolysis.

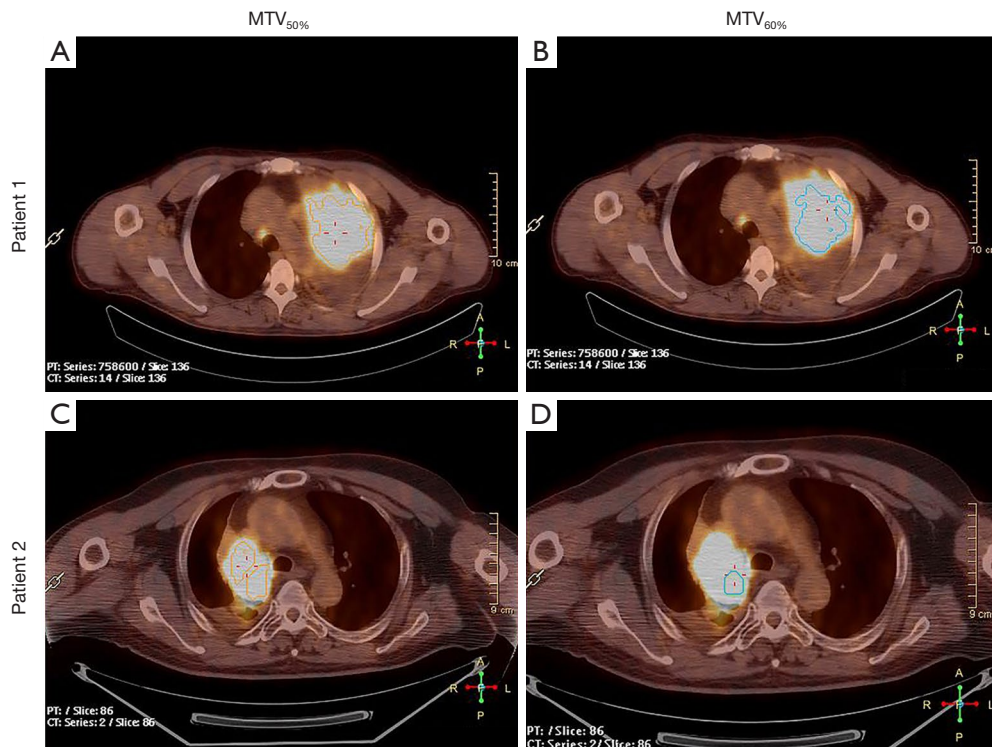


Figure 2 Representative FDG PET/CT images of two patients shown with MTV_{50%} and MTV_{60%}. The yellow lines indicate the MTV_{50%}, and the blue lines indicate the MTV_{60%}. They had similar MTV_{50%} (A: 37.4 mL vs. C: 34.6 mL). One patient's PFS was 7 months with MTV_{60%} of 21.2 mL (B). The other patient's PFS was 13 months with MTV_{60%} of 10.4 mL (D). MTV, metabolic tumor volume; PFS, progression-free survival.

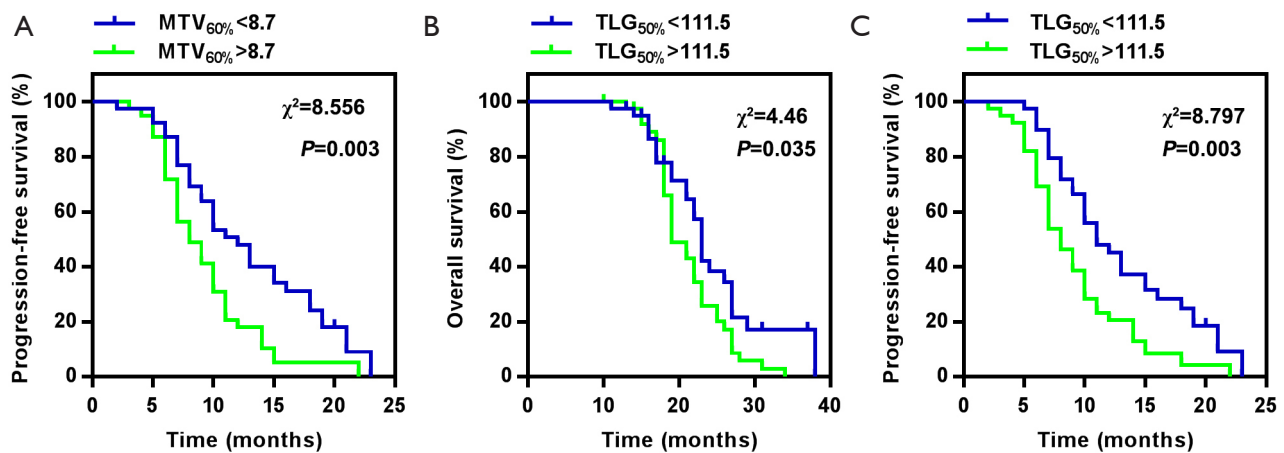


Figure 3 Kaplan-Meier survival curves for progression-free survival and overall survival. (A,C) Progression-free survival analyses based on MTV_{60%} (A) and TLG_{50%} (C). (B) Overall survival analysis based on TLG_{50%}. MTV, metabolic tumor volume; TLG, total lesion glycolysis.

MTV_{50%} is significantly associated with decreased OS in a subgroup of patients who were treated definitively (9). In another study, Hyun *et al.* demonstrated that MTV_{2.5} has been identified as an important prognostic factor for survival in stage IIIA NSCLC for patients treated with surgical resection (10). Our results are inconsistent with results from previous studies (9,10,20,26). We considered that there might be two reasons for this discrepancy. First, the previous studies used one of the standards of the MTV for the prognostic analysis, for instance, MTV_{2.5}, or MTV_{50%}, because it was used to approximate the TV (9,10,28). Furthermore, the previous studies did not perform comparative analysis among different levels of the MTV. In contrast, we analyzed a series of SUV thresholds of the MTV, comprising MTV_{2.5}, MTV_{40%}, MTV_{50%}, MTV_{60%}, MTV_{70%}, MTV_{80%}, and MTV_{90%}. To some extent, our analysis may complement previous results. However, MTV_{60%} is a TV fraction with a higher tumor metabolism than MTV_{2.5} or MTV_{50%}. Some studies have indicated that the FDG uptake is positively correlated with the biological aggressiveness and prognosis in NSCLC (11,29). Hence, it is possible that MTV_{60%} may represent a collection of more aggressive tumor cells than MTV_{40%}, MTV_{50%}, or MTV_{2.5}, while MTV_{70%}, MTV_{80%} and MTV_{90%} were relatively small in size, sometimes only a few voxels in PET/CT. Hence, for analyzing partial volume effects, their numerical values were not stable enough to serve as a prognostic factor.

In our previous study, we showed that the tumor sizes in CT are larger but similar to the pathology sizes (30). Kim *et al.* demonstrated that the lesion size of primary tumor, i.e., maximal tumor diameter as determined by pathological

findings cannot predict recurrence in pN0 NSCLC patients who have undergone curative surgery (31). Soussan *et al.* reported that baseline CTV was not a prognostic factor in stage III NSCLC treated with induction chemotherapy (32). We obtained the similar conclusion that CTV was not a prognostic factor. The reason may be that the intratumoral heterogeneity of local advanced NSCLC would be more conspicuous, consequently, to some extent, CTV cannot reflect the real TV, for example, partial necrosis of tumor would be involved in the CTV. In the contrast, it was reasonable that MTV_{60%} was a prognostic factor because it may represent the more aggressive sub-volumes of the tumor.

Soussan *et al.* used two segmentation methods, adaptive methods and fit methods, which were described respectively by Nestle *et al.* and Tylski *et al.*, for tumor delineation in their studies (32,33). The two methods have been previously reported to be reliable and robust in a large variety of tumor configurations (34,35). Soussan *et al.* reported that TV and TLG ratios helped predict residual viable tumor to preoperative chemotherapy in locally advanced NSCLC (33). The strength of this study was the use of precise method for delineating tumor, thorough tumor sampling and analysis of all available slides to reliably determine the amount of residual tumor cells (33). Since insufficient conditions on in-house algorithms, regretfully, we did not use these methods to delineate the TV. Instead of that, we calculated MTVs automatically on the PET/CT images with the specified SUV and delineated the TV on the CT scan. To some extent, the relative threshold method for defining MTV possibly reflects the most

metabolically active areas within each lesion (25), while the CTV represented an approximate size of TV. It was correspondent with our aim of the research, which was focused more on the prognostic value of the sub-volumes of the primary tumor compared with the whole TV.

According to our observations, the tumor shapes were variable and asymmetrical, and a high metabolic volume of the tumor was not always located in the center of the tumor, because the tumor composition and intratumoral 18F-FDG uptake are heterogeneous (3). AUC-CSH was known to reflect the tumor heterogeneity and lower AUC corresponding to higher degrees of heterogeneity (23). Kang *et al.* reported lower AUC-CSH could predict early disease progression in pretreatment FDG PET in inoperable stage III NSCLC (24). We did not obtain the consistent conclusion in our investigation. In our opinion, the most probably reason may be the larger proportion of primary tumors of T3/T4 in our cohort, and the small size of the sample. A large number of clinical trials and abundant basic research will be necessary in the future.

TLG combines volumetric and metabolic information and may more closely represent the tumor burden. Some studies have postulated that the summation of the tumor glycolysis, embodied by TLG, may be a good indicator for survival (26,36). Takahashi *et al.* showed that MTV was a prognostic factor for OS of patients with stage I lung cancer treated with SBRT. In the study, 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 for LC was $TLG_{40\%}$, followed by $TLG_{50\%}$ and $TLG_{60\%}$ (37). Satoh *et al.* have reported that $TLG_{50\%}$ and $TLG_{60\%}$ are significantly correlated with survival in early-stage NSCLC treated with SBRT, and this result has been found to be consistent when the tumor diameter is larger than 3 cm (8). Thus, we wondered whether $TLG_{50\%}$ and $TLG_{60\%}$ might have similar prognostic values for stage III NSCLC. Our results showed that $TLG_{50\%}$ was a significant predictor of OS and PFS [HR =0.423, P=0.023; HR =0.457, $P_{(TLG_{50\%})}$ =0.029]. As a prognostic factor, TLG is advantageous because of its simple and quick method of data collection. The results were obtained by a computer-based methodology, and the differences among observers were limited. These aspects enabled the efficient collection of tumor burden measurements (within approximately 1–2 min).

SUV_{max} as a prognostic factor for lung cancer has been subject to extensive research and debate (38–41). SUV_{max} has been found to be significantly related with NSCLC

prognosis in some studies (38,40). Satoh *et al.* reported that SUV_{max} has been found to be associated with the prognosis when the diameter of the primary tumor is less than 3 cm in the early stage of NSCLC (8). Some studies have suggested that SUV_{max} is not an independent prognostic factor for NSCLC, especially in advanced lung cancer research (26,42). Lin *et al.* have demonstrated that in patients treated with radical RT for inoperable NSCLC, higher SUV_{max} derived from a staging FDG-PET/CT scan does not significantly correlate with poorer survival (43). We obtained a similar result in our paper: SUV_{max} was not an independent prognostic factor for nonsurgical stage III NSCLC in terms of the OS or PFS (HR =0.885, P=0.717; HR =0.928 P=0.809). We considered some possible reasons. SUV_{max} represents only the metabolic value of a point in the tumor lesions, and thus this parameter cannot represent the malignance degree or biological characteristics of the entire tumor. Moreover, the value is vulnerable to statistical noise.

Our research has several limitations that need to be acknowledged. First, this study was a retrospective analysis with a small sample size. Although the study included patients with stage III NSCLC exclusively, the chemoradiotherapy regimens were not exactly the same, thus possibly confounding the analysis of the prognosis. Additionally, the results may be biased because of the relatively small sample size. Thus, a further prospective large-sample analysis is required. Second, the MTV values described in the current study are specific to the primary tumor, excluding the hilar or mediastinal metastatic lymph nodes, etc. Additionally, in some cases, the boundary between the primary tumor and the metastatic lymph nodes was not sufficiently clear. As a result, the MTV included the local metastatic lymph nodes at times. Finally, the partial volume effect of the PET/CT affected the analysis result to some extent. A few of the primary tumors were small; therefore, the higher metabolic volumes, such as $MTV_{70\%}$, $MTV_{80\%}$ or $MTV_{90\%}$, were smaller. The results of the statistical analysis may thus have been affected to some degree.

Conclusions

Volume-based PET pretreatment parameters have prognostic value in nonsurgical stage III NSCLC. The prognosis analysis using different thresholds is important. A higher value of $MTV_{60\%}$ predicts a worse PFS, and $TLG_{50\%}$ has a negative correlation with both OS and PFS. These results would be helpful to identify proper cohorts for

individualized therapeutic schedules, and need to be further investigated in larger cohorts in future trials.

Acknowledgments

Funding: This study was funded by the special fund for Scientific Research in the Public Interest (201402011).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2017.06.52>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Committee of the Cancer Hospital of Shandong Province, and all the patients signed informed consent (ID of Ethics Approval: 201208020).

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Cite this article as: Jie Y, Meng X, Gu A, Sun X, Yu J. Metabolic volume parameters based on different thresholds with baseline 18F-FDG PET/CT as prognostic factors for survival in stage III non-small cell lung cancer. *Transl Cancer Res* 2017;6(4):732-745. doi: 10.21037/tcr.2017.06.52