# Quantitative $^{18}$F-FDG PET analysis in survival rate prediction of patients with non-small cell lung cancer

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**Abstract.** The aim of the present study was to investigate the prognostic value of quantitative [$^{18}$F]fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) parameters for patients with non-small cell lung cancer (NSCLC). The present study conducted a retrospective review of the medical records of 203 patients with NSCLC, of which 193 patients underwent baseline $^{18}$F-FDG PET/CT prior to initial therapy. Multivariate analyses using Cox's proportional hazards regression were performed for the assessment of the association between initial PET/CT measurements and overall survival (OS). The multivariate models were adjusted for sex, age, smoking status, disease stage, standardized uptake value (SUV), standardized uptake value corrected for lean body mass (SUL), metabolic tumor volume (MTV), total lesion glycolysis (TLG) and standard deviation of SUV (SD). Kaplan-Meier (K-M) estimator curves were constructed following the formation of three approximately equal-sized groups using tertiles for each PET/CT measurement (n=65, 64 and 64). OS curves were plotted using K-M estimator curves. Results demonstrated significant associations between OS and MTV$_{PET\ volume\ computerized\ assisted\ reporting\ (PETVCAR)}$, MTV2.5, MTV25%, MTV42% and TLG$_{PETVCAR}$; however, no significant associations were identified between OS and MTV50%, MTV75%, TLG2.5, all SUV and SUL. Subgroup analyses according to pathology demonstrated that there were statistically significant associations between OS and stage (P<0.001), MTV50% (P=0.002) and MTV42% (P=0.004) in the adenocarcinoma group, and SUL$_{mean}$ (P=0.010), MTV25% (P=0.005) and MTV42% (P=0.001) in the squamous cell

carcinoma group; however, no significant differences were identified between any other group. Furthermore, there was a significant association between OS and MTV42% (P=0.02) and MTV50% (P=0.04) in the early-stage group; however, no significant differences were identified in the advanced-stage group. K-M estimator curve analyses demonstrated that the pathology (P=0.01), stage (P<0.001) and all PET metabolic parameters with the exception of SD were significantly associated with OS (P<0.05). No significant associations were demonstrated between SD and OS. In conclusion, $^{18}$F-FDG PET/CT MTV$_{PETVCAR}$, MTV2.5, MTV25%, MTV42% and TLG$_{PETVCAR}$ exhibit prognostic values with regard to OS. Overall, selection of appropriate metabolic parameters may predict NSCLC prognosis.

## Introduction

Lung cancer is the leading cause of cancer-associated mortality worldwide, of which non-small cell lung cancer (NSCLC) accounts for ~80% of all cases (1). Survival rate analyses of patients with lung cancer have become a key point of interest in recent years. Survival rates of patients with NSCLC are associated with early diagnosis and treatment, as well as a number of other factors including the stage of the disease, which is based on the evaluation of the tumor (T), node (N) and metastasis (M) grading system, and the assignment of disease staging (I-IV) (2). Collectively, these factors are important in determining patient prognosis; however, it is important to note that numerous patients presenting at early stage are capable of relapse (3,4).

Currently, lung cancer-associated pathological differences are not yet well-established; however, [$^{18}$F]fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET)/computed tomography (CT) may be a useful tool in observing tumor characteristics and patient prognosis non-invasively. Metabolic tumor burden measurements including metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been developed previously, which provide information on tumor volume and metabolic activity, respectively (5,6). Despite previous studies demonstrating the superiority of MTV and/or TLG calculations compared with the maximum standardized uptake value (SUV$_{max}$) for measuring tumor burden, the practicality of using MTV and/or TLG has not been without controversy (7). In

addition, PET Response Criteria In Solid Tumors (PERCIST) 1.0 recommends that the standardized uptake value corrected for lean body mass $(SUL)_{peak}$ should replace the traditional standardized uptake value $(SUV)_{max}$; however, an association between SUL and long-term survival rates has not yet been demonstrated. Furthermore, intratumoral heterogeneity characterized by PET has demonstrated a predictive and prognostic value over SUV measurements (8,9). In the present study, the prognostic value of $^{18}$F-FDG PET/CT parameters, including $SUV_{max}$, $SUV_{mean}$, $SUL_{max}$, $SUL_{mean}$, $SUL_{peak}$, MTV and TLG, were investigated for the management of patients with NSCLC.

## Materials and methods

*Patients*. The present study was approved by the Institutional Review Board of Tianjin Medical University Cancer Institute and Hospital (Tianjin, China). A retrospective review of the medical records of patients with NSCLC who had undergone baseline $^{18}$F-FDG-PET/CT prior to initial therapy was conducted. Written informed consent was obtained from each patient prior to each PET/CT scan. All patients were followed up for ≥5 years after surgery. A total of 203 consecutive patients (62.05±10.78 years) who were pathologically diagnosed with NSCLC at Tianjin Medical University Cancer Institute and Hospital (Tianjin, China) between February 2004 and August 2010 were included in the present study. Inclusion criteria included: i) All patients had a pre-therapy baseline PET/CT scan; ii) primary lung cancer was treated using surgery; iii) patients had no history or concurrent diagnosis of another type of cancer; and iv) patients were followed up for ≥5 years after surgery.

*PET/CT protocol*. All patients were required to fast for ≥6 h prior to the 60 min uptake period of $^{18}$F-FDG (3.70-4.81 mBq/kg). Blood glucose was measured using a finger blood test (CNGQFOC8, UltraVue; Johnson & Johnson, Shanghai, China) prior to the injection to ensure that levels were <6.8 mmol/l. Scanning was performed from head to thigh using a PET/CT system (Discovery ST4; GE Healthcare, Chicago, IL, USA). The protocol included an initial CT scan followed by PET acquisition. The initial CT was performed at 120 kV and 100 mA, and the slice thickness was 5 mm. PET data were obtained in three-dimensional mode with an acquisition time of 2 min for each bed, with between 6 and 8 bed positions being completed. PET images were reconstructed with attenuation correction calculated from co-registered CT images using ordered subset expectation maximization (OSEM) iterative algorithm (10). Following completion of acquisition, separate PET images, CT images and fused PET/CT data were available for review in coronal, sagittal and axial planes using an Xeleris review station (GE Healthcare) and PET volume computerized assisted reporting (PETVCAR) on an Advantage Workstation (version 4.6; GE Healthcare,) (11) was used to analyze results.

*Image analysis*. Images were observed using a Xeleris review station, which allowed visualization of PET/CT and fused sections in transverse, coronal and sagittal planes. Images were interpreted by two board-certified nuclear medicine physicians who were informed of patients' clinical data at the time of scanning; however, they were not aware of the patient outcome.

Metabolic characteristics of lung cancer using $^{18}$F-FDG uptake assisted in defining the volume of interest (VOI) metabolic parameter, which was created over the lung cancer (>0.5 cm in diameter) using PETVCAR on an Advantage Workstation (version 4.6; GE Healthcare). PETVCAR is an automated segmentation software system that uses an iterative adaptive algorithm to detect the threshold level; this separates the target volume from the background tissue by determining the $SUV_{max}$ and the $SUV_{mean}$ within a target volume, with a weighting factor of 0.5 (12). A VOI was placed around the primary tumor to ensure that all the tumor activity was within the VOI, while avoiding regions of physiologically increased activity (e.g. $^{18}$F-FDG uptake in the heart). If high-activity structures could not be avoided, they were removed prior to analysis.

When segmentation is at an estimated threshold, PETVCAR was used to calculate the following parameters for lung cancer VOI: $SUV_{max}$ and $SUL_{max}$ were defined as the maximum SUV and SUL, respectively, within the target volume, and were derived from the single voxel with the highest tracer uptake within the VOI; $SUV_{mean}$ and $SUL_{mean}$ were calculated as the sum of SUV or SUL in each voxel within the target volume, divided by the number of voxels within the target volume, which were derived from all voxels within the VOI, assuming that it reflected the tracer uptake within that VOI; $SUL_{peak}$ was defined as the largest possible mean value of a 1 cm$^3$ spherical region of interest (ROI) within a tumor; $MTV_{PETVCAR}$ represented the contoured tumor tissues with accumulation of $^{18}$F-FDG; $TLG_{PETVCAR}$ was defined as the product of $SUV_{mean}$ and MTV; SD was defined as the standard deviation of SUV.

Once segmentation had reached the maximum percentage threshold, PETVCAR was used to calculate several parameters for lung cancer VOI, including MTV25, MTV42, MTV50 and MTV75%, which were defined as tumor volume with an absolute threshold of 25, 42, 50 and 75% of the histogram of $SUV_{max}$, respectively.

When segmentation was at a fixed threshold (SUV>2.5), PETVCAR was used to calculate several parameters for lung cancer VOI, including MTV2.5, and TLG2.5. MTV2.5 was defined as tumor volume with SUV >2.5 being the absolute threshold, whereas TLG2.5 was defined as the product of $SUV_{mean}$ and MTV2.5.

*Lung cancer staging*. Disease staging was determined according to the TNM staging system and PET/CT results. Brain magnetic resonance imaging scans were performed in order to detect any potential brain metastases. If patients had undergone a mediastinoscopy, these results superseded the imaging results in mediastinum nodal staging. Tumor location was divided into right upper lung, right middle lung, right lower lung, left upper lung, left lower lung and double lung. According to the different pathological types, all patients with NSCLC were divided into three groups: Adenocarcinoma, squamous cell carcinoma and others.

*Statistical analysis*. Multivariate analyses using Cox's proportional hazards regression were performed for the assessment

of the association between initial PET/CT measurements and overall survival (OS). Multivariate models were adjusted for sex, age, smoking status, disease staging, $SUV_{mean}$, $SUV_{max}$, $SUL_{mean}$, $SUL_{max}$, $SUL_{peak}$, $MTV_{PETVCAR}$, MTV2.5, MTV25%, MTV42%, MTV50%, MTV75%, $TLG_{PETVCAR}$, TLG2.5 and SD. K-M estimator curves were constructed following the production of three approximately equal-sized groups (n=65, 64 and 64) using tertiles from each PET/CT measurement, and the differences in survival rates within these groups were assessed using the log-rank test. OS curves were plotted using the K-M estimator method, and the differences in survival rates within these groups were assessed using the log-rank test. Statistical analysis was used to assess whether these new measurements provided any additional information regarding patient survival rates compared with the risk factor provided by assessing the cancer stage. OS was calculated from the date of surgery to the last follow-up or the time of patient mortality. P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS (version 17.0; SPSS, Inc., Chicago, IL, USA).

## Results

*Patient characteristics.* In total, 203 patients fulfilled the inclusion criteria, of which 114 were adenocarcinoma, 66 were squamous cell carcinoma, 10 were adenosquamous carcinoma, 4 were large cell carcinoma, 3 were atypical carcinoid, 2 were poorly differentiated mucous epidermoid carcinoma, 2 were lymphoepithelioma-like carcinoma and 2 were sarcomatoid carcinoma (Table I).

*Survival rate analyses.* The 5-year survival rate of 203 patients was 57±3% (mean ± standard error of the mean). The 95% confidence interval for the 5-year cumulative survival rate of patients was 62.88 and 51.11%.

Multivariate models were adjusted for different pathological types, sex, age, smoking status, disease stage and tumor location in 203 patients. Results demonstrated a significant association between OS and pathological types (P=0.01), and also stage (P<0.001); however, no significant differences were identified between OS and sex, age, smoking status and/or location. In total, 9 patients with adenocarcinoma and 1 patient with squamous cell carcinoma were associated with undetectable levels of $^{18}$F-FDG uptake (Table II); therefore $^{18}$F-FDG parameters were measured in 193 patients. Results demonstrated significant associations between OS and disease stage [P<0.001; odds ratio (OR)=1.414], $MTV_{PETVCAR}$ (P=0.002; OR=0.987), MTV2.5 (P=0.009; OR=0.948), MTV25% (P=0.003; OR=1.055), MTV42% (P=0.04; OR=0.907) and $TLG_{PETVCAR}$ (P=0.003; OR=1.016). Results presented little difference between OR values and survival rates, which suggests that the influence of various parameters on survival rates are similar; however, no significant associations were identified between OS and MTV50, MTV75%, TLG2.5, all SUV and/or SUL.

According to the results obtained from pathological analysis, 193 patients were divided into three groups: Adenocarcinoma, squamous cell carcinoma and others. Cox's multivariate analyses were performed regarding OS adjusted for stage, $SUV_{mean}$, $SUV_{max}$, $SUL_{mean}$, $SUL_{max}$, $SUL_{peak}$, $MTV_{PETVCAR}$, MTV2.5,

Table I. Patient characteristics.

| Variables | No. of patients | Proportion, % |
|---|---|---|
| Sex | | |
| Male | 116 | 57.1 |
| Female | 87 | 42.9 |
| Histology | | |
| Adenocarcinoma | 114 | 56.2 |
| Squamous cell carcinoma | 66 | 32.5 |
| Others | 23 | 11.3 |
| Smoking history | | |
| Adenocarcinoma | 44 | 38.6 |
| Squamous cell carcinoma | 58 | 87.9 |
| Others | 17 | 73.9 |
| Stage | | |
| IA | 72 | 35.5 |
| IB | 32 | 15.8 |
| IIA | 33 | 16.3 |
| IIB | 9 | 4.4 |
| IIIA | 34 | 16.7 |
| IIIB | 7 | 3.4 |
| IV | 16 | 7.9 |
| Tumor location | | |
| RUL | 60 | 29.6 |
| RML | 17 | 8.4 |
| RLL | 36 | 17.7 |
| LUL | 48 | 23.6 |
| LLL | 41 | 20.2 |
| DL | 1 | 0.5 |

RUL, right upper lung; RML, right middle lung; RLL, right lower lung; LUL, left upper lung; LLL, left lower lung; DL, double lung.

MTV25, MTV42, MTV50, MTV75%, $TLG_{PETVCAR}$, TLG2.5 and SD within each group, respectively. Results obtained from the adenocarcinoma group demonstrated significant associations between OS and stage (P<0.001), MTV50% (P=0.002) and MTV42% (P=0.004). Results obtained from the squamous cell carcinoma group demonstrated significant associations between OS and $SUL_{mean}$ (P=0.010), MTV25% (P=0.005) and MTV42% (P=0.001). Results obtained from the others group demonstrated no significance between OS and all other parameters.

In total, 193 patients were divided into early-stage (I and II; n=140) and late-stage (III and IV; n=53). Cox's multivariate analyses were performed with regard to OS adjusted for stage, $SUV_{mean}$, $SUV_{max}$, $SUL_{mean}$, $SUL_{max}$, $SUL_{peak}$, $MTV_{PETVCAR}$, MTV2.5, MTV25%, MTV42%, MTV50%, MTV75%, $TLG_{PETVCAR}$, TLG2.5 and SD within each group, respectively. Results from the early-stage group demonstrated significant associations between OS, MTV42% (P=0.02; OR=1.572) and MTV50% (P=0.04; OR=0.871).

Table II. Characteristics of PET-negative patients with NSCLC.

| Status | Time, months | Stage | Smoking status | Sex | Age, years |
|---|---|---|---|---|---|
| Alive | 22.57 | IIIA | Yes | Female | 57 |
| Deceased | 24.90 | IA | No | Male | 58 |
| Deceased | 38.50 | IIIA | Yes | Male | 47 |
| Alive | 39.33 | IIIA | Yes | Female | 62 |
| Deceased | 64.30 | IA | Yes | Female | 47 |
| Deceased | 64.33 | IV | Yes | Female | 57 |
| Deceased | 83.67 | IA | Yes | Female | 50 |
| Alive | 94.60 | IA | No | Male | 57 |
| Alive | 108.00 | IA | Yes | Female | 55 |

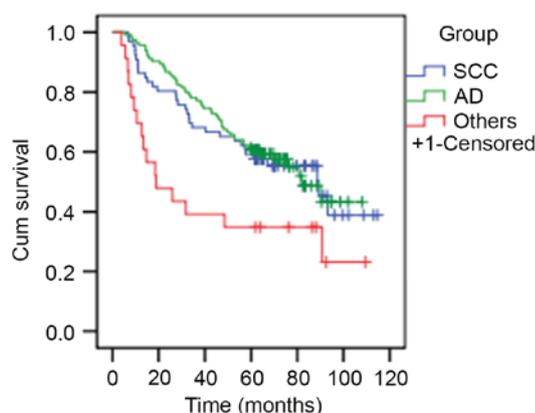PET, positron emission tomography; NSCLC, non-small cell lung cancer.



Figure 1. Survival rate curves for patients with SCC, AD and others. SCC, squamous cell carcinoma; AD, adenocarcinoma; Cum, cumulative.

Patients with squamous cell carcinoma or adenocarcinoma exhibited significantly increased median survival rates compared with patients within the others group (89.37, 81.80 and 18.93 months, respectively; P=0.009; Fig. 1).

The median survival rate of patients was 83.6 months at stage IA, >60 months at stage IB, 67.07 months at stage IIA, >60 months at stage IIB, 57.60 months at stage IIIA, 27.13 months at stage IIIB and 32.5 months at stage IV. These results were statistically significant (P=0.013). The median survival rates for patients was 88.67 months at stage I, 67.07 months at stage II, 48.05 months at stage III and 32.5 months at stage IV. These results were also statistically significant (P=0.02). The median survival rate of patients who presented at an early-stage was significantly increased compared with patients who presented at a late stage (88.67 vs. 40.33 months, respectively; P=0.02). The survival curves are presented in Fig. 2. K-M estimator curves were constructed following the formation of three approximately equal-sized groups using tertiles from PET/CT indices. Results are presented in Table III, with representative survival rate curves presented in Fig. 3. Results demonstrated statistical significance among all PET/CT indices with the exception of SD. Furthermore, results demonstrated that as OS decreases, metabolism increases.
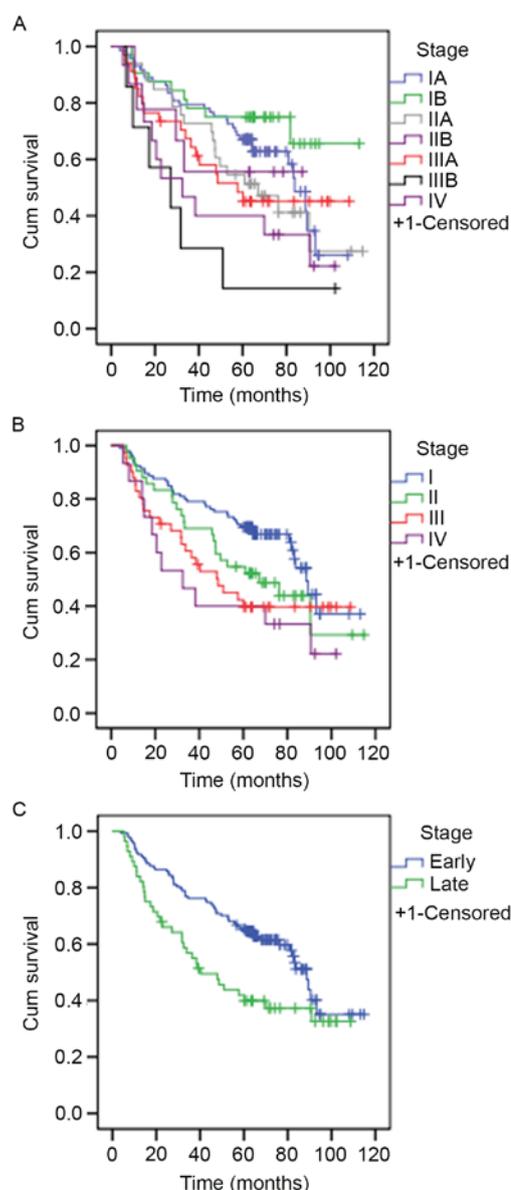


Figure 2. Survival rate curves for patients with NSCLC. (A) Stage IA, IB, IIA, IIB, IIIA, IIIB and IV. (B) Stages I-IV. (C) Early and late stage. Cum, cumulative.

Table III. Results from Kaplan-Meier estimator curves following the formation of three approximately equal-sized groups using tertiles from each PET/CT indices.

| PET metabolic index | Log-rank test | P-value |
|---|---|---|
| $MTV_{PETVCAR}$ | 21.709 | <0.001 |
| MTV2.5 | 21.389 | <0.001 |
| MTV25% | 28.489 | <0.001 |
| MTV42% | 19.709 | <0.001 |
| MTV50% | 20.099 | <0.001 |
| MTV75% | 18.154 | <0.001 |
| $TLG_{PETVCAR}$ | 27.084 | <0.001 |
| TLG 2.5 | 30.520 | <0.001 |
| $SUV_{max}$ | 7.942 | 0.019 |
| $SUV_{mean}$ | 8.224 | 0.016 |
| $SUL_{max}$ | 15.337 | <0.001 |
| $SUL_{mean}$ | 7.628 | 0.022 |
| $SUL_{peak}$ | 17.489 | <0.001 |
| SD | 4.591 | 0.101 |

PET, positron emission tomography; CT, computerized tomography; MTV, metabolic tumor volume; PETVCAR, PET volume computerized assisted reporting; TLG, total lesion glycolysis; SUV, standardized uptake volume; SUL, standardized uptake value corrected for lean body mass; SD, standard deviation of standardized uptake volume; max, maximum.

## Discussion

In the present study, the prognostic value of $^{18}$F-FDG PET/CT metabolic parameters was investigated. The Cox's multivariate models demonstrated that there were significant associations between OS and various pathological parameters and disease stages. The results of the present study are in agreement with those of previous studies, which demonstrate that TNM staging may serve as a prognostic marker for patients with lung cancer (2,13-15). However, results demonstrated no significant associations between OS and sex, age, smoking status or tumor location. This is not in agreement with previous studies, which have demonstrated an association between these parameters and survival rates (16-18). A number of studies have discussed the association between tumor location regarding pre-treatment images and prognosis; however, the results differed. Lally et al (19) reported that the location of the main bronchus was one of primary risks associated with mortality; however, Bandoh et al (20) demonstrated that no significant difference in prognosis was identified between the peripheral and central types of lung cancer.

Cox's multivariate analyses using PET metabolic indices demonstrated significant associations between OS and $MTV_{PETVCAR}$, MTV2.5, MTV25%, MTV42% or $TLG_{PETVCAR}$; however, no significant differences were identified between OS and MTV50%, MTV75%, TLG2.5, or all SUV and SUL. Therefore, these results suggest that MTV and TLG are improved prognostic markers for patients with lung cancer compared with SUV and SUL measurements. $^{18}$F-FDG PET/CT-based imaging parameters including $SUV_{max}$, MTV and TLG have been previously suggested as potential prognostic markers for various types of neoplasm (21-24). This may be due to SUV and SUL being a single voxel value, and therefore may not represent total tumor metabolism. However, accumulating evidence suggests that MTV and TLG are superior in assessing NSCLC response compared with $SUV_{max}$; however, the efficient determination of these values is not yet well-established (1,25-29). Results from recent studies demonstrate that MTV and TLG were computed using a maximum percentage threshold of 40-50% (30,31). However, other studies used a fixed SUV threshold, most commonly SUV2.5, where SUV>2.5 is the absolute threshold (TLG2.5 or MTV2.5), particularly for segmentation of lung tumors (32-34). Increasing interest in volumetric indices has led to the development of commercially available tools, for example PETVCAR, which enables the rapid and simple measurement of numerous indices for tumor analysis, including various threshold values of MTV and TLG (typically, 41-70% of $SUV_{max}$ within the tumor) (35). However, there are also several conflicting results regarding the prognostic value of volumetric parameters in NSCLC (36,37). Furthermore, the association between survival rates and SUL remains unclear.

Results from subgroup data with regard to pathology analysis demonstrated that patients with adenocarcinoma exhibited a significant association between OS and stage, MTV50% or MTV42%; patients with squamous cell carcinoma exhibited significant associations between OS and $SUL_{mean}$, MTV25% or MTV42%; patients assigned to the others group did not exhibit any significant associations. Early stage Cox's multivariate analyses demonstrated significant associations between OS and MTV42% or MTV50%; however, no significant differences were identified in late-stage Cox's multivariate analyses. Therefore, MTV50% and/or MTV42% in adenocarcinoma or early stage, and MTV25% and/or MTV42% in squamous cell carcinoma may provide an improved prediction of prognosis compared with other metabolic indexes ($SUV_{mean}$, $SUV_{max}$, $SUL_{mean}$, $SUL_{max}$, $SUL_{peak}$, $MTV_{PETVCAR}$, MTV2.5, MTV75%, $TLG_{PETVCAR}$, TLG2.5 and SD) for patients with NSCLC. In 2013, Machtay et al (38) conducted a large prospective multi-center study investigating 250 patients with stage III NSCLC and demonstrated that pretreatment $SUV_{max}$ was not associated with survival rates.

K-M estimator analyses demonstrated that the pathology, stage and all PET metabolic parameters with the exception of SD were significantly associated with OS. These results are not in agreement with those obtained from the Cox's multivariate analyses. The K-M survival rate curves of a number of indexes had a common crossover point, that may have lead to the different results of K-M estimator analyses and the Cox. Furthermore, previous studies investigating the use of PET intratumoral heterogeneity characterization demonstrated a potential added predictive and prognostic value over simple SUV measurements (8,9). However, SD demonstrated no significant association with OS in the Cox's multivariate analyses or the K-M log-rank test.

It is important to note that the present study has several limitations. First, the retrospective nature has resulted in numerous
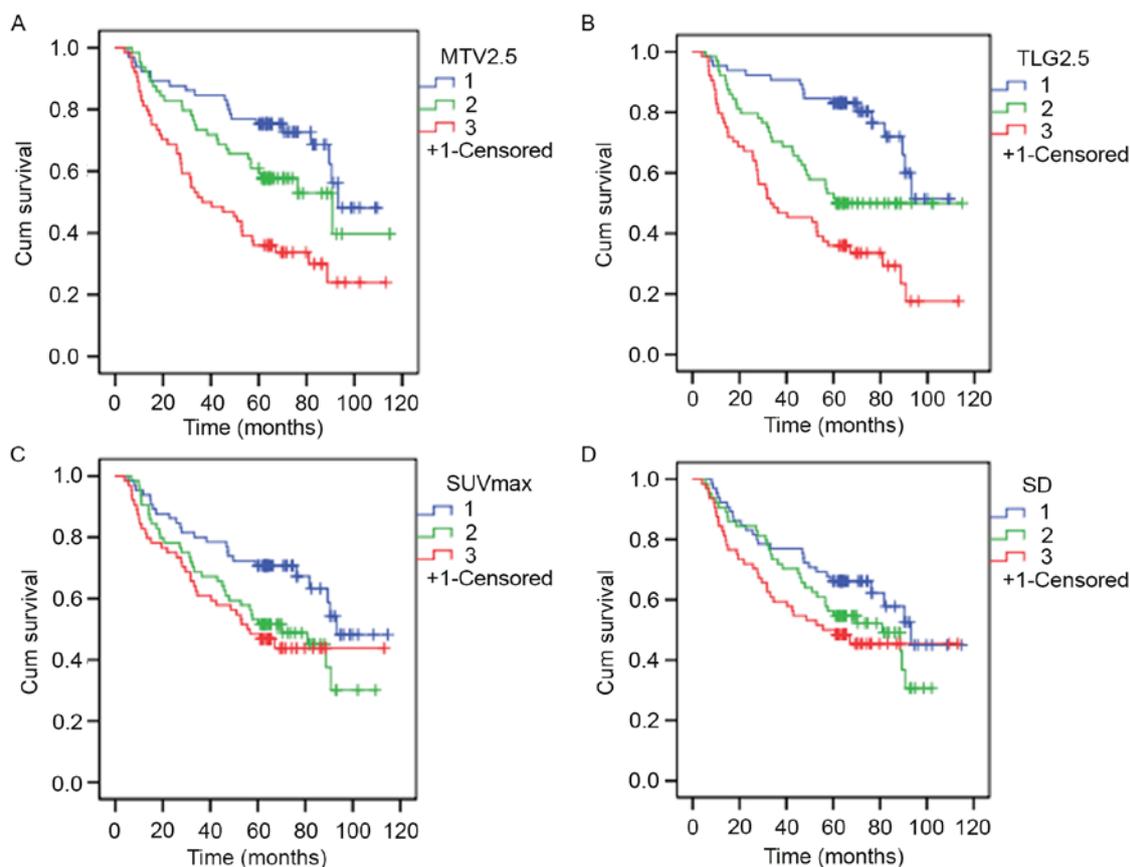
Figure 3. Survival rate curves following the formation of three approximately equal-sized groups using tertiles from each PET/CT index. Results demonstrate statistically significant associations between OS and (A) MTV2.5, (B) TLG2.5 or (C) SUV$_{max}$, but (D) no significant association between OS and SD. PET, positron emission tomography; CT, computerized tomography; MTV2.5, metabolic tumor volume >2.5; TLG2.5, total lesion glycolysis >2.5; SUV$_{max}$, maximum standardized uptake volume; SD, standard deviation of standardized uptake volume; Cum, cumulative.

biases including the fact that patient characteristics may not be representative of an entire population. Secondly, the present study was performed at a single hospital, and therefore results are not representative of national or international populations. Thirdly, all patients had undergone primary lung cancer surgery, which may induce results bias. Therefore, prospective large-scale multicenter studies with longer follow-up periods and patients that have undergone various types of therapy are required to identify the prognostic markers of post-surgical outcomes.

In conclusion, ^{18}F-FDG PET/CT quantitative parameters including MTV$_{PETVCAR}$, MTV2.5, MTV25, MTV42% and TLG$_{PETVCAR}$ exhibit prognostic value for OS; however, MTV50, MTV75%, TLG2.5, SD, all SUV and SUL do not. There were certain differences within the subgroups. Selection of appropriate metabolic parameters may be useful in predicting prognosis for future patients with NSCLC.

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## Funding

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

WX and WM designed this study and prepared this manuscript; MW, XL, HH, YZ, XS, DD collected clinical samples and analyzed data.

## Ethics approval and consent to participate

The present study was approved by the Department of Molecular Imaging and Nuclear Medicine, Tianjin Medical University Cancer Institute and Hospital (Tianjin, China) and written informed consent was obtained from all patients.

## Patient consent for publication

Written informed consent was obtained from all participants prior to publication.

## Competing interests

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