Original Article

# Prognostic Value of Metabolic Tumor Parameters in Pretreatment $^{18}$F-Fluorodeoxyglucose Positron Emission Tomography–Computed Tomography Scan in Advanced Non-Small Cell Lung Cancer

**Ayan Mallick, Jayanta Das, Manoj Kumar Shaw, Bivas Biswas[1], Soumendranath Ray**

*Departments of Nuclear Medicine and PET-CT and [1]Medical Oncology, Tata Medical Center, Kolkata, West Bengal, India*

## Abstract

**Objective:** This retrospective study aimed to investigate whether metabolic parameters of primary tumour i.e. maximum standardized uptake value (SUVmax), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) predict overall survival (OS) in patients with advanced stage non-small cell lung cancer (NSCLC). **Materials and Methods:** SUVmax, MTV and TLG of the primary tumors were measured in staging $^{18}$F-Fluorodeoxyglucose Positron emission tomography- Computed tomography ($^{18}$F-FDG PET/CT) scan of 97 NSCLC patients by gradient based tumour segmentation method. Prognostic ability was assessed for overall survival (OS) of the patients. **Result:** The median follow-up period of the study was 15.84 months (range 1.3 to 47.97 months).The estimated median OS was 11.29 months (range 1.37 to 38.63 months). Total of 40 (41.24%) patients had progressive disease and 21 (21.65%) patients died during the follow up period. Receiver Operating Characteristic (ROC) analysis showed that the area under the curve (AUC) for MTV was significant (area = 0.652 ± 0.065; 95% CI = 0.548 – 0.746; $P$ = 0.020). Kaplan-Meier survival curves showed that the OS differences between the groups of patients who were dichotomized by the median value of MTV (38.76 ml, $P$ = 0.0150) and TLG (301.69 ml, $P$ = 0.0046) were significant. MTV (hazard ratio = 4.524; 95% CI = 1.244 – 16.451; $P$ = 0.022) was found to be an independent prognostic factor for OS in multivariate analysis. **Conclusion:** MTV of the primary tumor is a potential prognostic parameter for OS in our population of advanced NSCLC patients independent of other risk factors.

**Keywords:** *Maximum standardized uptake value, metabolic tumor volume, non-small cell lung cancer, overall survival, positron emission tomography, prognostic factors*

## Introduction

Lung cancer is the leading cause of cancer incidence and cancer-related mortality worldwide.[1] Globally, lung cancer accounted for 2.1 million new cases and 1.8 million deaths in 2018 alone, representing 18.4% of total cancer-related deaths.[2] According to GLOBOCAN 2018 (global cancer incidence, mortality, and prevalence) report produced by the International Agency for Research on Cancer, lung cancer constitutes 5.9% of all new cancer cases and 9.3% of all cancer-related deaths in both sexes in India.[3] It is the most common form of cancer and the leading cause of cancer related mortality in men. The established prognostic factors for non-small cell lung cancer (NSCLC) are primary staging, performance status (Karnofsky scale), and histopathological subtype.[4-7] The primary imaging modality used for staging of localized NSCLC is $^{18}$F-fluorodeoxyglucose positron emission tomography–computed tomography ($^{18}$F-FDG PET/CT) scan. It combines functional and anatomic assessment.[8] It offers superior accuracy for describing primary lesions measuring more than 1 cm, all locoregional lymph nodes, and distant metastasis except the brain, for which magnetic resonance imaging (MRI) is warranted.[9] With the increasing interest in the prognostic value of metabolic parameters of tumors, $^{18}$F-FDG PET/CT has become the standard of care not only in the initial staging of NSCLC but also for restaging and treatment monitoring.[10,11]

FDG uptake in tumors is proportional to the metabolic rate of viable tumor cells and hence might help in the prediction of the biologic aggressiveness of a tumor.[12]

***Address for correspondence:***
*Dr. Jayanta Das, Department of Nuclear Medicine and PET-CT, Tata Medical Center, Kolkata - 700 084, West Bengal, India.*
*E-mail: Jayanta.das@tmckolkata.com*

**Received:** 28-07-2020
**Revised:** 04-08-2020
**Accepted:** 18-08-2020
**Published:** 21-06-2021

**Access this article online**

**Website:** www.ijnm.in

**DOI:** 10.4103/ijnm.IJNM_170_20

**Quick Response Code:**



**How to cite this article:** Mallick A, Das J, Shaw MK, Biswas B, Ray S. Prognostic value of metabolic tumor parameters in pretreatment $^{18}$F-fluorodeoxyglucose positron emission tomography–computed tomography scan in advanced non-small cell lung cancer. Indian J Nucl Med 2021;36:107-13.

Therefore, it was postulated that by offering information regarding metabolic activity, the staging $^{18}$F-FDG PET/CT scan may be useful in predicting the response to therapy, at least in selected situations.[13] Previous studies have focused mainly on the maximum standardized uptake value (SUVmax). In various staged and treated populations, the potential prognostic value of SUVmax for primary lung cancer was widely reported.[14] SUVmax represents a single voxel within the tumor which corresponds with maximum metabolic activity. It fails to represent the overall metabolic tumor behavior.[15] Volumetric measurements of metabolic tumor burden, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), are more realistic representations of metabolic activity. MTV and TLG have been proven to be significant prognostic factors in patients with NSCLC, independent of TNM stage.[16]

### Objectives

The purpose of this study was to investigate whether metabolic parameters of primary tumor, i.e., SUVmax, MTV, and TLG, predict overall survival (OS) in patients with advanced stage NSCLC.

## Materials and Methods

### Study design and inclusion and exclusion criteria

Approval was obtained from the institutional review board, and the informed consent requirements were waived in view of retrospective nature of the study. All patients had confirmed the histological diagnosis of NSCLC to appropriate immunohistochemistry, and a staging $^{18}$F-FDG PET/CT examination was done at our institution before initiation of therapy. Patients who had completed initial treatment were included in this study. Patients with dual primary were excluded from this analysis. Patients were clinically followed up at regular intervals and CT scan of chest was done for response assessment using Response Evaluation Criteria of Solid Tumor version 1.1 (RECIST 1.1).[17] Imaging was also done in patients who exhibited symptoms concerning disease progression.

### Patient preparation

After overnight fasting, patients were taken for a whole-body $^{18}$F-FDG PET/CT scan. Age, height, weight, and blood glucose levels were recorded. The mean blood glucose level was 100.3 ± 16.1 (standard deviation) mg/dL. Patients were injected with a mean FDG dose of 12.3 ± 2.6 mCi (455.1 ± 96.2 MBq) intravenously about an hour before scan.

### Acquisition of $^{18}$F-fluorodeoxyglucose positron emission tomography–computed tomography data

All PET/CT scans were done in Discovery STE 64 scanner (GE Healthcare, Illinois, USA). All patients were scanned from the skull base to the mid-thigh. Unenhanced CT scan was used for PET attenuation correction. PET scans were obtained using 3D imaging with emission scans

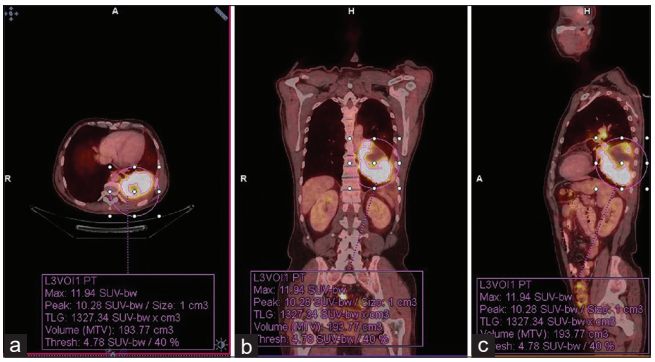


**Figure 1: (a) Axial, (b) coronal, (c) sagittal fused positron emission tomography–computed tomography image of primary lung cancer with region of interest showing metabolic tumor parameters, i.e., maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG)**

that ranged from 2 to 4 min per bed position with an field of view (FOV) of 50 cm. PET scan slices were 3.27 mm thick and reconstructed every 3.27 mm. Contrast-enhanced CT scans of the same area were obtained and fused after matching the PET scans' FOV and slice thickness.

### Interpretation of positron emission tomography–computed tomography images and measurement of tumor volume

CT attenuation-corrected FDG-PET images were reconstructed using an ordered subset expectation maximization algorithm (28 subsets, 2 iterations). Images were displayed in a 128 × 128 matrix (pixel size 4.29 × 4.29 mm, slice thickness 4.25 mm). CT and FDG-PET scan data were accurately co-registered on a workstation using ADW software (GE Healthcare, Illinois, USA). FDG-PET/CT images were reviewed by nuclear medicine physicians and a radiologist who had no knowledge of the clinical information. Target lesions were determined to be primary tumors based on FDG uptake and anatomical location. SUVmax, MTV, and TLG of primary lesions of lung were measured using fixed threshold-based tumor segmentation method [Figure 1].

- Standardized uptake value (SUV) – SUV is a mathematically derived ratio of radioactivity concentration in a tissue at a certain point in time C (t) to the injected dose of radioactivity per kg of the patient's body weight. It is considered a semi-quantitative value as it is vulnerable to other variabilities[15]
- Metabolic tumor volume (MTV) – It is the volume inside an algorithm- or user-defined region of interest (ROI) that segments the metabolically active tumor. To determine the boundaries of the ROI, threshold-based or algorithm-based methods have been proposed and evaluated[16]
- TLG – It is representative of the metabolic activity defined throughout the entire tumor and is calculated by multiplying MTV and the SUVmean.[18] TLG = MTV × SUVmean

### Statistical analysis

Descriptive analysis was used for clinical and treatment parameters. OS was defined as the time from initial PET/CT examination until the death from any cause. For survivors, survival time was censored at the last date that the patient was known to be alive. The data were last updated on 31 March 2020. Survival analysis was carried out using the Kaplan–Meier method with a log-rank test to assess differences between groups. The median values of metabolic tumor parameters of primary lesion were considered as cutoff values.

Receiver operating characteristic (ROC) analysis was performed for SUVmax, MTV, and TLG of primary tumor in respect to OS (null hypothesis: area = 0.5, i.e., ROC curve coinciding with the diagonal reference line).

Univariate and multivariate analyses were performed using Cox proportional hazards models to identify the independent prognostic factors for OS. The prognostic factors analyzed included MTV, TLG, SUVmax, AJCC prognostic stage group, tumor histological subtype, and treatment method. In the multivariate analysis, a forward stepwise method was applied to assess the potential independent effects of metabolic parameters for OS. A correlation coefficient matrix was calculated to address the problem of multicollinearity before undertaking the multivariate Cox regression analysis.

All statistical analyses were performed using MedCalc Version 19.3 (MedCalc Software Ltd, Windows version released in November 1996, Ostend, Belgium). $P$ =0.050 was selected as the threshold of statistical significance.

## Results

### Patient characteristics

The demographic and clinical characteristics of the patients are presented in Table 1. This study involved 97 patients with a median age of 65 years (range: 19–79 years) and male: female ratio of 73:24. The major histological subtypes identified were adenocarcinoma in 53 patients (54.64%) and squamous cell carcinoma in 38 patients (39.18%). A summary of the metabolic characteristics of primary tumors is enlisted in Table 2. Fifty-three patients had Stage III disease while 44 patients had Stage IV disease. Ten patients had only intrathoracic metastasis. Seven patients had single extrathoracic metastatic lesion and another 27 patients had multiple extrathoracic metastases. Brain metastases were correlated with MRI findings.

Forty-five patients (46.39%) got curative intent treatment. Eleven patients got stereotactic body radiation therapy (SBRT) to primary tumor. Combined chemoradiation therapy (CTRT) was given in 28 patients and surgery was done on 6 patients. On the other hand, 52 (53.60%) were given palliative care. Among them, 38 patients were treated with palliative chemotherapy. Nine patients got immunotherapy with erlotinib or gefitinib. Other modalities of palliative treatment were instituted on 5 patients.

40 (41.24%) Patients had disease progression during follow-up, while 21 (21.65%) died within this time period. Patients succumbed to the disease in each group according to cutoff values of metabolic tumor parameters evaluated are shown in Table 3. The estimated median OS was 11.29 months (range, 1.37–38.63 months). The median follow-up period of the study was 15.84 months (range, 1.3–47.97 months).

In ROC curve analysis, the area under the curve for SUVmax was 0.559 ± 0.072 (95% confidence interval [CI] ranged from 0.454 to 0.660; $P$ = 0.413) for MTV, it was recorded to be 0.652 ± 0.065 (95% CI ranged from

**Table 1: Patients' demographic and clinical characteristics**

| Clinical parameters | Number of patients (%) |
|---|---|
| Gender | |
| Male | 73 (75.25) |
| Female | 24 (24.75) |
| Age (years) | |
| >60 | 63 (64.95) |
| ≤60 | 34 (35.05) |
| Tumor histology | |
| Adenocarcinoma | 53 (54.64) |
| Squamous cell carcinoma | 38 (39.18) |
| Others | 6 (6.18) |
| Smoking history | |
| Present | 56 (57.73) |
| Absent | 34 (35.05) |
| Not known | 7 (7.22) |
| AJCC staging | |
| IIIA | 21 (21.64) |
| IIIB | 18 (18.56) |
| IIIC | 14 (14.43) |
| IVA | 17 (17.53) |
| IVB | 27 (27.84) |
| Treatment intent | |
| Curative | 45 (46.39) |
| Palliative | 52 (53.60) |
| Survival outcome | |
| Alive | 76 (78.35) |
| Death | 21 (21.65) |

ACCJ: American Joint Committee on Cancer

**Table 2: Metabolic parameters of primary tumor**

| PET parameters | Median | Range |
|---|---|---|
| SUVmax | 12.55 | 1.60-22.80 |
| MTV (in ml) | 38.76 | 3.70-638.00 |
| TLG (in ml) | 301.69 | 6.07-5614.40 |

SUVmax: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

0.548 to 0.746; $P$ = 0.020) [Figure 2], and for TLG, the value was 0.595 ± 0.066 (95% CI ranged from 0.490 to 0.694; $P$ = 0.150) for differentiating those who had died at the end of follow-up from those still alive. The median SUVmax cutoff point of 12.55 had a sensitivity, specificity, and likelihood ratio (LR) 54.79, 69.57, and 1.80, respectively. The median MTV cutoff point of 38.76 ml has a sensitivity, specificity, and LR 57.53, 60.87, and 1.47, respectively. The median TLG cutoff point of 301.69 ml has a sensitivity, specificity, and LR 52.00, 52.83, and 1.09, respectively. (All data are expressed in 100-point scale of ROC curve.) The area under the ROC curve for MTV was significantly different from the reference area of 0.5, and hence, we can conclude that there is evidence of MTV having an ability to predict the OS in patients ($P$ < 0.05).

Kaplan–Meier survival curves were generated for patients who were dichotomized by the median value of SUVmax, MTV, and TLG of primary tumor as threshold values. OS curves were compared using the Mantel–Cox log-rank test. Figure 3a shows lower OS among patients with SUVmax ≥ 12.55, when compared to those with SUVmax < 12.55 ($P$ = 0.1246). Figure 3b shows significantly lower OS among patients with MTV ≥ 38.76 ml, when compared to those MTV < 38.76 ml (P = 0.0150). Figure 3c shows significantly lower OS among patients with TLG ≥ 301.69 ml, when compared to those with TLG < 301.69 ml ($P$ = 0.0046). Therefore, the PET parameters, namely MTV and TLG, significantly differentiated OS based on the respective cutoff values (for both $P$ < 0.05).

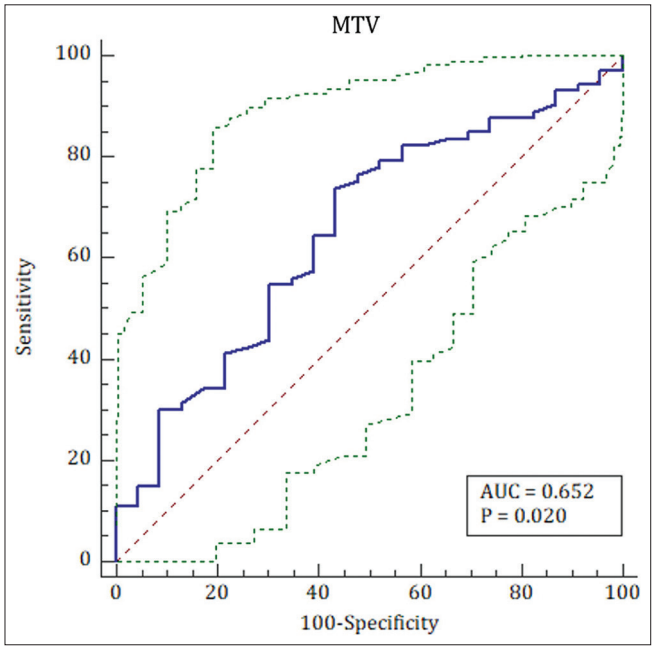


**Figure 2: Receiver operating characteristic curve shows area under the curve for metabolic tumor volume. It was recorded to be 0.652 ± 0.065 ($P$ = 0.020)**

Univariate Cox proportional hazards model analysis showed that N stage, M stage, MTV, and TLG were significant prognostic factors for the OS of the patients ($P$ < 0.05 for all), whereas patient sex and age, tumor histological subtype, and SUVmax were not significantly associated with the OS of the patients ($P$ > 0.05 for all). To further evaluate the effects of the clinical and PET parameters on the OS of the patients, multivariate Cox proportional hazards model analysis was performed, using forward stepwise selection to construct the final model, including significant variables. For OS, MTV remained statistically significant ($P$ < 0.05) in both the models. The Hazard Ratio (HR) for MTV was recorded to be 4.524 (95% CI was 1.244–16.451; $P$ = 0.022). A summary of the univariate and multivariate Cox proportional hazards model analysis of potential prognostic factors influencing the OS of 97 patients is enlisted in Table 4.

## Discussion

In this exploratory retrospective study, the prognostic values of various metabolic parameters of primary tumor,

**Table 3: Patients succumbed to the disease in each group (according to cutoff values of parameters evaluated)**

| Metabolic parameter | Value | Alive | Dead |
|---|---|---|---|
| SUVmax | ≤12.55 | 39 | 9 |
| | >12.55 | 36 | 12 |
| MTV | ≤38.76 | 36 | 12 |
| | >38.76 | 39 | 9 |
| TLG (in ml) | ≤301.79 | 38 | 10 |
| | >301.79 | 37 | 11 |

SUVmax: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

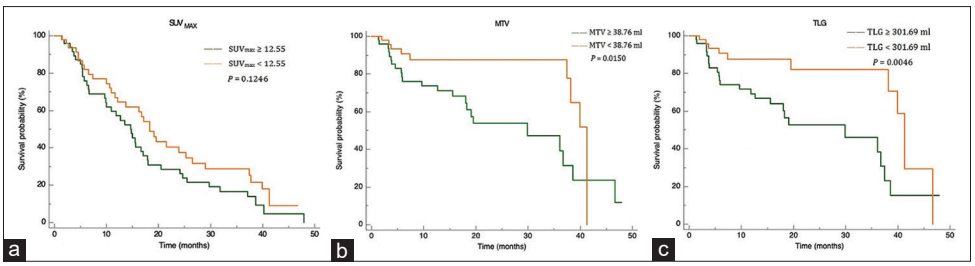


**Figure 3: (a) Lower overall survival (OS) among patients with SUVmax ≥ 12.55, when compared to those with SUVmax <12.55 ($P$ = 0.1246). (b) Significantly lower OS among patients with MTV ≥38.76 ml, when compared to those MTV <38.76 ml ($P$ = 0.0150). (c) Significantly lower OS among patients with TLG ≥301.69 ml, when compared to those with TLG <301.69 ml ($P$ = 0.0046)**

**Table 4: Univariate and multivariate Cox proportional hazards model analysis of potential prognostic factors influencing the overall survival**

| Parameters | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *P* | Hazard ratio | 95% CI | *P* |
| Patient characteristics | | | | | | |
| Age (>60 years vs. ≤60 years) | 1.220 | 0.669-2.223 | 0.516 | | | |
| Sex (male vs. female) | 1.679 | 0.610-4.619 | 0.315 | | | |
| Tumor histological subtype | | | | | | |
| Adenocarcinoma vs. others | 0.648 | 0.351-1.196 | 0.165 | | | |
| TNM staging | | | | | | |
| N stage (N2/N3 vs. N0/N1) | 2.064 | 1.093-3.900 | 0.026 | 1.225 | 0.339-4.418 | 0.756 |
| M stage (M1 vs. M0) | 1.950 | 1.039-3.660 | 0.038 | 0.627 | 0.243-0.162 | 0.335 |
| Metabolic parameters | | | | | | |
| SUVmax (≥12.55 vs. <12.55) | 1.432 | 0.904-2.269 | 0.124 | | | |
| MTV (≥38.76 ml vs. <38.76 ml) | 2.421 | 1.188-4.935 | 0.015 | 4.524 | 1.244-16.451 | 0.022 |
| TLG (≥301.69 ml vs. <301.69 ml) | 2.690 | 1.358-5.329 | 0.005 | 0.356 | 0.092-1.374 | 0.067 |

SUVmax: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, CI: Confidence interval, TNM: Tumor, node, and metastasis

**Table 5: Prognostic value of metabolic tumor burden in different studies**

| Author | Study population | Metabolic parameters | Outcome variables | Result | Reference |
|---|---|---|---|---|---|
| Lee *et al*. | 18 NSCLC | MTV and SUV of whole body | TTP and OS | MTV is an independent poor prognostic factor | [19] |
| Zhang *et al*. | 104 surgical NSCLC | MTV and TLG of whole body | OS | MTV and TLG are independent poor prognostic factors | [20] |
| Liao *et al*. | 169 non-surgical NSCLC | MTV and TLG of whole body, primary tumor, node, and metastasis | OS | MTV and TLG have statistically significant association with OS | [21] |
| Kim *et al*. | 91 surgical NSCLC | MTV and TLG of primary tumor | RFS and OS | MTV2.5 was revealed as a significant prognostic factor for RFS | [22] |
| Davidson *et al*. | 39 NSCLC | MTV and TLG of primary lesion | 12-month survival and OS | MTV and TLG have statistically significant association with OS<br>MTV associated with 12-month mortality | [23] |

NSCLC: Non-small cell lung cancer, MTV: Metabolic tumor volume, SUV: Standardized uptake value, TTP: Time to progression, OS: Overall survival, TLG: Total lesion glycolysis, RFS: Recurrence-free survival

such as SUVmax, MTV, and TLG have been investigated. Among them, it was found that only MTV of primary tumor was the independent prognostic factor for OS of advanced NSCLC.

The first study which showed that baseline whole-body MTV measured semi-automatically was a statistically significant indicator of prognosis in 19 patients with lung cancer and it was proved to be better than SUVmax and SUVmean was performed by Lee *et al*.[19] Multiple studies that aimed at evaluating the prognostic value of MTV and TLG have shown that these measures were either more accurate than SUVmax and/or SUVmean or they are the sole prognostic marker of outcome in NSCLC [Table 5].

A study of 270 consecutive patients diagnosed with NSCLC demonstrated that MTV of the primary tumor and nodal metastasis, in combination with the number of lymph nodes that tested positive, is a more important prognostic factor than TNM staging for OS of patients with inoperable NSCLC treated with chemoradiation.[24] Another study focused mainly on the patients with adenocarcinoma. In univariate and multivariate analysis, both high MTV and TLG values were found to be independent predictors of poor overall and progression-free survival in the patients who suffered from advanced stages of the disease (Stage III and IV).[25]

This exploratory retrospective study detected MTV of primary lesion as an independent prognostic indicator of OS in NSCLC. At univariate analysis, MTV, TLG, N stage, and M stage had a statistically significant inverse correlation with OS. However, at multivariate analysis, only MTV remained statistically significant, whereas TLG was very close to significance level. The study was unable to find any statistically significant association between SUVmax or TLG and the OS of the patients with NSCLC. SUVmax is a

maximum single-voxel measurement, and hence, it may not represent the entire tumor biological activity. In addition, it does not represent the total extent of the tumor burden. Although TLG incorporates the information imparted by MTV, in multivariate analysis, it was also not statistically significantly associated with the OS in this cohort of patients diagnosed with NSCLC. The lack of statistical significance is most likely due to the small sample size in the study. This study thus indicated the importance of using both metabolic and volumetric information to predict the prognosis.

### Limitations

It is a retrospective study. Treatment for each of the patients was determined at the discretion of the surgeon and/or oncologist and finally by the patient. Hence, a prospective randomized study is needed for the validation of the results. The study had a relatively small sample size in the subgroup analysis. It renders the statistical power insufficient to determine the optimal cutoff values. A larger cohort will help define the relationship in the lower range of MTV values better. Third, PET/CT has limited sensitivity to detect the lesions that are <1 cm in diameter or those who have low metabolic uptake, which may have resulted in slightly distorted measurements of MTV and TLG. Fourth, high FDG accumulation is not only limited to the malignant tissues. It has been shown by previous studies that high FDG uptake was associated with tumor-associated macrophages and young granulation tissues than in the tumor cells themselves.[26] Thus, MTV and TLG might be overestimated; however, MTV proved to be a good indicator of prognosis in this study. One limitation is that we have not included molecular driven mutation and the treatment in the model. MTV may lose its importance in molecular driven tumors. It needs further research.

### Scope of further study

Currently, there is no consensus on how exactly the measurements of metabolic tumor burden should be used in everyday clinical practice. It is also unclear how sensitive the values of MTV and TLG are to the FDG uptake time. What are the effects of different PET/CT scanners and reconstruction methods on the values of MTV and TLG are also unexplored. These basic questions need to be addressed properly with additional research before any wider application of these metabolic tumor burden parameters that take place in the management of patients diagnosed with NSCLC. Prospective randomized clinical trials need to be conducted that utilizes the metabolic tumor burden measures. An additional future goal is the development of more reliable computer-assisted diagnostic which will aid in reporting automated, accurate, and reproducible values and also important to study these parameters in those receiving targeted therapy or immunotherapy.

## Conclusion

Our study showed a significant prognostic value of MTV of primary tumor in advanced stage of NSCLC. MTV was additionally found to be the only metabolic parameter associated with the OS of the patients independent of patient age and sex, TNM stage, treatment, and tumor histology. Thus, it can be clearly concluded from this study that MTV is an independent potential prognostic indicator in patients diagnosed with NSCLC and thus could be an important guide for treatment decisions. It was also observed that high TLG value of primary tumors in this study is significantly associated with low OS, but this needs further validation by prospective study with larger patient population.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## References

1. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer 2001;37 Suppl 8:S4-66.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer J Clin 2018;68:394-424.
3. Dar MA, Sharma KK. Burden of cancer in India: GLOBOCAN 2018 estimates. J Emerging Technol Innovative Res 2019;6:505-14.
4. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8th lung cancer TNM classification and clinical staging system: Review of the changes and clinical implications. Quant Imaging Med Surg 2018;8:709-18.
5. Karnofsky DA, Abelmann WH, Craver LF and Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma – With particular reference to bronchogenic carcinoma. Cancer 1948;1:634-56.
6. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group (ECOG). Am J Clin Oncol 1982;5:649-55.
7. Rinaldi S, Berardi R. Lung cancer prognosis: Can histological patterns and morphological features have a role in the management of lung cancer patients? Ann Transl Med 2017;5:353.
8. Gregory DL, Hicks RJ, Hogg A, Binns DS, Shum PL, Milner A, *et al*. Effect of PET/CT on management of patients with non-small cell lung cancer: Results of a prospective study with 5-year survival data. J Nucl Med 2012;53:1007-15.
9. Cuaron J, Dunphy M, Rimner A. Role of FDG-PET scans in staging, response assessment, and follow-up care for non-small cell lung cancer. Front Oncol 2012;2:208.
10. Hicks RJ, Kalff V, MacManus MP, Ware RE, McKenzie AF, Matthews JP, *et al*. The utility of (18) F-FDG PET for suspected recurrent non-small cell lung cancer after potentially curative therapy: Impact on management and prognostic stratification. J Nucl Med 2001;42:1605-13.
11. Hoekstra CJ, Stroobants SG, Hoekstra OS, Vansteenkiste J,

Biesma B, Schramel FJ, *et al*. The value of [18F] fluoro-2-deoxy-D-glucose positron emission tomography in the selection of patients with stage IIIA-N2 non-small cell lung cancer for combined modality treatment. Lung Cancer 2003;39:151-7.

12. Dosani M, Yang R, McLay M, Wilson D, Liu M, Yong-Hing CJ, *et al*. Metabolic tumour volume is prognostic in patients with non-small-cell lung cancer treated with stereotactic ablative radiotherapy. Curr Oncol 2019;26:e57-63.
13. Paesmans M, Berghmans T, Dusart M, Garcia C, Hossein-Foucher C, Lafitte JJ, *et al*. Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer: Update of a systematic review and meta-analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project. J Thorac Oncol 2010;5:612-9.
14. Sasaki R, Komaki R, Macapinlac H, Erasmus J, Allen P, Forster K, *et al*. [18F] fluorodeoxyglucose uptake by positron emission tomography predicts outcome of non-small-cell lung cancer. J Clin Oncol 2005;23:1136-43.
15. Obara P, Pu Y. Prognostic value of metabolic tumor burden in lung cancer. Chin J Cancer Res 2013;25:615-22.
16. Chen HH, Chiu NT, Su WC, Guo HR, Lee BF. Prognostic value of whole body total lesion glycolysis at pre-treatment FDG PET/CT in NSCLC. Radiology 2012;264:559-66.
17. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European J Cancer 2009;45:228-47.
18. Olivier A, Petyt G, Cortot A, Scherpereel A, Hossein-Foucher C. Higher predictive value of tumour and node [18 F] FDG PET metabolic volume and TLG in advanced lung cancer under chemotherapy. Nucl Med Communications 2014;35:908-15.
19. Lee P, Weerasuriya DK, Lavori PW, Quon A, Hara W, Maxim PG, *et al*. Metabolic tumor burden predicts for disease progression and death in lung cancer. Int J Radiat Oncol Biol Phys 2007;69:328-33.
20. Zhang H, Wroblewski K, Liao S, Penney BC, Zhang Y, Pu Y, *et al.* Prognostic value of metabolic tumor burden from 18F FDG PET in surgical patients with non small cell lung cancer. Acta Radiol 2013;20:32-40.
21. Liao S, Penney BC, Wroblewski K, Zhang H, Simon CA, Kampalath R, *et al*. Prognostic value of metabolic tumor burden on 18F FDG PET in non surgical patients with non small cell lung cancer. Europ J Nucl Med Molecular Imaging 2012;39:27 38.
22. Kim K, Kim SJ, Kim IJ, Kim YS, Pak K, Kim H. Prognostic value of volumetric parameters measured by F-18 FDG PET/CT in surgically resected non-small-cell lung cancer. Nucl Med Commun 2012;33:613-20.
23. Davison J, Mercier G, Russo G, Subramaniam RM. PET-based primary tumor volumetric parameters and survival of patients with non-small cell lung carcinoma. AJR Am J Roentgenol 2013;200:635-40.
24. Dehing-Oberije C, De Ruysscher D, van der Weide H, Hochstenbag M, Bootsma G, Geraedts W, *et al*. Tumor volume combined with number of positive lymph node stations is a more important prognostic factor than TNM stage for survival of non-small-cell lung cancer patients treated with (chemo) radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:1039-44.
25. Chung HW, Lee KY, Kim HJ, Kim WS, So Y. FDG PET/CT metabolic tumor volume and total lesion glycolysis predict prognosis in patients with advanced lung adenocarcinoma. J Cancer Res Clin Oncol 2014;140:89-98.
26. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose *in vivo*: High accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33:1972-80.