Article published online: 2022-04-19

Original Article

Prognostic value of metabolic parameters measured by ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography in surgically resected non-small cell lung cancer patients

ABSTRACT

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography-derived metabolic parameters can play a role in prognostication. We investigated the prognostic value of various metabolic parameters such as maximum standardized uptake value (SUV_{max}), mean SUV (SUV_{mean}), whole-body metabolic tumor volume (WBMTV), and whole-body total lesion glycolysis (WBTLG) in surgically resected non-small cell lung cancer (NSCLC) patients. We retrospectively reviewed 153 patients with NSCLC who underwent surgical resection. The SUV_{max}, SUV_{mean}, WBMTV, and WBTLG of the tumor were measured. Continuous PET parameters were stratified by receiver operating characteristic curve analysis. Prognostic factors were estimated using the Kaplan–Meier method and Cox proportional hazards model. The median follow-up was 36.9 months. Fifty-six patients died and 78 patients had recurrence. On univariate analysis, tumor-node-metastasis (TNM) stage; male sex; no adjuvant treatment; and higher SUV_{max}, SUV_{mean}, WBMTV, and WBTLG were statistically significant and were associated with poor overall survival (OS). TNM stage; no adjuvant treatment; and higher SUV_{max}, SUV mean, WBMTV, and WBTLG were statistically significant and were associated with poor disease-free survival (DFS). On multivariate analysis, higher WBTLG (hazard ratio [HR] = 3.08, $P = 0.007$) for DFS and higher WBTLG (HR = 2.70, $P = 0.041$) and TNM staging (HR = 1.63, $P = 0.035$) for OS were statistically significant. Whole-body tumor burden assessment with TLG has independent prognostic value in patients with operated lung cancer. Incorporation of TLG into clinical practice can identify patients benefitted from additional therapy.

Keywords: ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography, lung cancer, metabolic parameters, prognostic value, total lesion glycolysis

INTRODUCTION

Lung cancer is one of the leading causes of cancer-associated mortality. Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases and the rest 10%–15% is constituted by SCLC. A combination of 18F fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) with contrast and magnetic resonance imaging of brain has become a standard practice in staging workup of lung cancer in several centers.[1] ^{18}F-FDG PET-CT in the initial evaluation will reduce futile thoracotomies by 20% by detecting remote metastases at an early stage.[2,3] Surgery, radiotherapy, and systemic therapy are the three main modalities used to treat

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Submitted: 24-Mar-2019, **Accepted:** 18-May-2019, **Published:** 27-Feb-2020

How to cite this article: Mathew B, Purandare NC, Puranik A, Shah S, Agrawal A, Pramesh CS, *et al.* Prognostic value of metabolic parameters measured by ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography in surgically resected non-small cell lung cancer patients. World J Nucl Med 2020;19:8-14.

Access this article online	
Website: www.wjnm.org	Quick Response Code
DOI: 10.4103/wjnm.WJNM_26_19	

NSCLC patients, either alone or in combination depending on the disease status. The outcomes of the lung cancer patients remain poor despite numerous recent advances in screening and diagnosis, molecular pathology, and therapeutic interventions; hence, a better understanding of the risk factors is needed for improving the outcome.[4] The prognostic factor that is regularly used is the tumor stage. However, there are multiple other tumor-related and treatment-related factors deciding the outcome of patients.[5,6] Other promising prognostic factor is tumor metabolism which can be evaluated by ^{18}F-FDG PET-CT.[7,8] ^{18}F-FDG PET-CT's potential to give information about the metabolism of the tumor has been used to prognosticate the patients. Metabolic parameters such as maximum standardized uptake value (SUV_{max}), mean SUV (SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) can be obtained from 18F-FDG PET-CT. A few studies have shown the correlation of these factors with survival in patients with NSCLC.[9-11] In our study, we evaluated the relative importance of these parameters in prognosticating surgically resected NSCLC.

MATERIALS AND METHODS

Patient characteristics

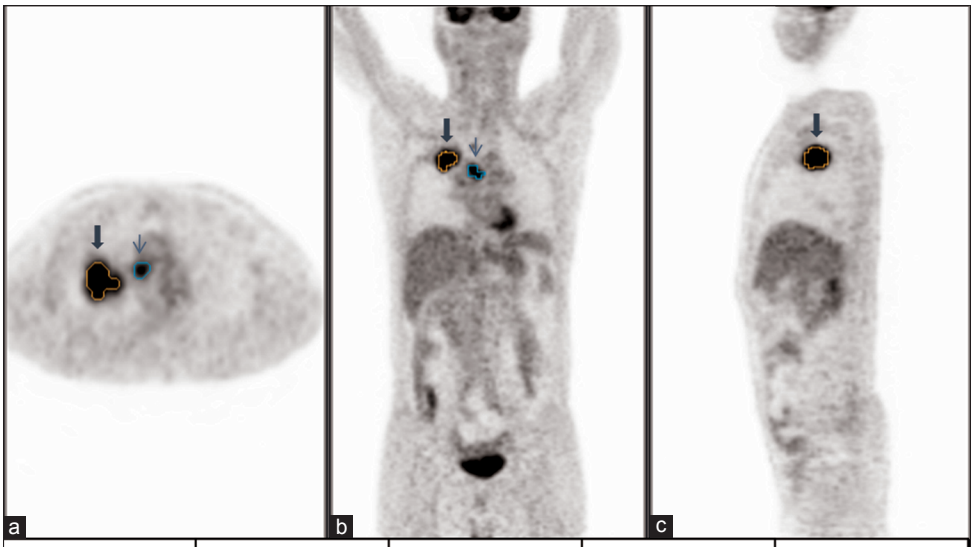
The institutional review board approved the retrospective study, and the waiver of informed consent was obtained (Project No. 1718/IEC-I/06-2016). The study population consisted of biopsy-proven NSCLC patients who underwent curative surgical resection from January 2009 to December 2013 at Tata Memorial Hospital, Mumbai. Inclusion in the study was in accordance with the following criteria. (1) biopsy-proven NSCLC, (2) patients who underwent a baseline ^{18}F-FDG PET-CT study at our hospital and whose ^{18}F-FDG PET-CT Digital Imaging and Communications in Medicine data were available, (3) no distant metastases, and (4) patients whose follow-up data were available. Patients who received prior cancer-directed treatment, with inoperable disease, medically unfit for resection, later diagnosed with second malignancy, and treated for a malignancy earlier were excluded from the study. All patients after completion of definite treatment were followed up as per institution protocol. We retrospectively reviewed the medical records, ^{18}F-FDG PET-CT, and pathology reports. Tumor-node-metastasis (TNM) staging was based on the American Joint Committee on Cancer 7th edition. Data were collected from medical records to determine recurrence or death, along with other clinicopathological characteristics. A diagnosis of disease recurrence was based on an unequivocal, either clinical or radiographic, evidence of any recurrence or a positive biopsy.

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography protocol

All patients were fasting for at least 6 h prior to the intravenous (IV) injection of 5MBq/kg body weight of ^{18}F-FDG. Blood glucose level was checked in patients with diabetes and patients who were not certain about their glycemic status. PET-CT examination was performed only when blood glucose level was below 180 mg/dl (10 mmol/L). The scanning field was base of skull to mid-thigh. The scans were performed using Philips Gemini TF TOF 16/64 PET CT scanners (PET crystal-LYSO) (Cleveland, OH, USA) at 60 ± 15 min after injection of ^{18}F-FDG. After obtaining a scout image, whole-body CT scanning was performed first in craniocaudal direction (120 kV, automated mA, slice thickness 5 mm, field of view (FOV) 600 mm, rotation time 0.5 s, and image matrix – 512 × 512) without any breath hold instructions. The images were reconstructed with a thickness of 2 mm. 80 ml of low osmolar nonionic IV contrast was administered in all eligible patients at a rate of 1.8 ml/s, and scan delay was 50 s. Contrast-enhanced CT was used for diagnostic purpose and for attenuation correction of the PET data. A separate sequence with breath holding was acquired for the evaluation of the lungs (120 kV, 250 mAs/slice, thickness – 3 mm, increment – 1.5 mm, and FOV of 300 mm). PET scanning was performed immediately after the CT acquisition, without changing the patient's position with an acquisition time of 60–90 s for each bed position. PET was acquired in three-dimensional mode. Images were reconstructed iteratively using row-action maximum likelihood algorithm. CT attenuation correction, dead time correction, and decay correction were applied.

Measurement of positron emission tomography parameters

All reconstructed images were viewed on display system having Extended Brilliance Workspace software (EBW) version 4.5.3.40140, Philips Healthcare (Cleveland, OH, USA). ^{18}F-FDG PET-CT studies were reviewed by two experienced nuclear medicine physicians. The reviewers reached a consensus in cases of any discrepancy. The SUV_{max}, SUV_{mean}, MTV, and TLG of the tumor were measured with tumor-tracking software in Philips EBW workstation. To define the contouring margins around the tumor, we used the gradient tumor segmentation method by using 40% of the maximum intratumoral activity. The volume of interest was drawn automatically after identifying the major and minor axes of the primary tumor and metastatic mediastinal lymph nodes (LNs) in each plane to incorporate each target lesion in the axial, coronal, and sagittal PET-CT. The software then automatically measured the SUV_{max}, SUV_{mean}, MTV, and TLG of the tumor and LNs [Figure 1]. SUV_{max} is the highest voxel value within the region of interest (ROI), which is defined as the maximum activity concentration in the tumor/(injected dose/



Lesion	SUVmax	SUVmean	MTV	TLG
Primary tumour	11.7	7.8	29.3	229.5
Nodes	7.6	4.1	6.3	30.0

Figure 1: A 61-year-old man with biopsy-proven adenocarcinoma of the right lung. Axial (a), coronal (b), and sagittal (c) images showing the measurement of metabolic parameters for the primary tumor (block arrow) and mediastinal nodes (arrow) using the tumor tracking software with results displayed below

body weight). SUV_{mean} is the average voxel value within the ROI, which is defined as the mean concentration of ^{18}F-FDG in the tumor/(injected dose/body weight). MTV is defined as the volume of tumor tissues with increased ^{18}F-FDG uptake above a fixed threshold. In our study, we took 40% of the maximum intratumoral activity as the threshold. TLG is defined as the product of MTV and average SUV (MTV × SUV_{mean}). Whole-body MTV (WBMTV) and whole-body total lesion glycolysis (WBTLG) were recorded as the sum of MTV of the primary tumor and mediastinal nodes and sum of TLG of the primary tumor and mediastinal nodes, respectively.

Statistical analysis

The metabolic parameters of SUV_{max}, SUV_{mean}, WBMTV, and WBTLG of the tumor obtained from ^{18}F-FDG PET CT were displayed as continuous variables. Clinical and pathological variables analyzed include age, sex, histology, type of surgery, TNM staging, neoadjuvant treatment, and adjuvant treatment. Overall survival (OS) was measured from the date of diagnosis to the date of death from any cause or the date at last clinical follow-up. Disease-free survival (DFS) was measured as the time between the date of diagnosis and the first recurrence of the disease. Receiver operating characteristic (ROC) curve analysis was used to derive optimal cutoffs for PET metabolic parameters. Continuous PET parameters were stratified using these cutoffs. The same cutoff value for each parameter was used to compare the OS and DFS in all analyses. Other variables were grouped into two categories for statistical analyses which include median age, sex, TNM stage, histology (adenocarcinoma vs. others), neoadjuvant treatment (none vs. yes), adjuvant therapy (none vs. yes), and type of surgery (lobectomy vs. pneumonectomy). In univariate analysis, survival curves were estimated using the Kaplan–Meier method for each variable and were compared using the log rank test to evaluate for any statistical significance. The Cox proportional hazards model was used in multivariate analysis with variables that showed statistical significance in univariate analysis to identify independent prognostic factors for OS and DFS. $P < 0.05$ was considered statistically significant. Statistical analyses were performed by using SPSS software version 21.0 (IBM, Armonk, NY, USA).

RESULTS

Patient characteristics

We identified 153 eligible patients, and there were 118 male and 35 female patients with a median age of 58 years (range 22–82 years). There were 42 cases with Stage I, 76 with Stage II, and 35 with Stage III NSCLC based on TNM staging. Among the histologic types, there were 96 adenocarcinomas, 44 squamous cell carcinomas, and 13 other histological variants. All patients had definitive surgery including lobectomy in 120 patients, bilobectomy in 14 patients, pneumonectomy in 17 patients, and wedge resection in 2 cases. At the time of analysis, 56 (36.6%) patients were dead and 78 (50.9%) had experienced recurrence after surgical resection. The median follow-up for surviving patients was 36.9 months (range 9.4–87.7 months). Neoadjuvant

therapy was administered to 32 patients and adjuvant therapy was administered postoperatively to 93 patients. Patients' characteristics are shown in Table 1.

Prognostic factors

The cutoff point chosen for PET-based parameters based on ROC curve analysis with area under curve was 15.48 (0.709), 8.89 (0.689), 34.77 (0.747), and 341.1 (0.766) for SUV_{max}, SUV_{mean}, WBMTV, and WBTLG, respectively. In the univariate analysis, TNM stage, male sex, no adjuvant treatment, higher SUV_{max}, higher SUV_{mean}, higher WBMTV, and higher WBTLG were statistically significant and were associated with poor OS. Whereas higher age, histological subtype, type of surgery, and neoadjuvant treatment were not statistically significant for poor OS. OS was 45.3 months, 45.6 months, 44.1 months, and 39.9 months in patients with values at or above the cutoff value for SUV_{max}, SUV_{mean}, WBMTV, and WBTLG, respectively ($P < 0.001$). OS was 69.1 months, 69.5 months, 72.6 months, and 72.6 months in patients with values below cutoff for SUV_{max}, SUV_{mean}, WBMTV, and WBTLG, respectively [Figure 2].

TNM stage, no adjuvant treatment, higher total SUV_{max}, higher SUV_{mean}, higher WBMTV, and higher WBTLG were statistically significant and associated with poor DFS. Whereas higher age, sex, histological subtype, type of surgery, and neoadjuvant treatment were not statistically significant for DFS. DFS was 36.8 months, 34.3 months, 36.2 months, and 29.1 months in patients with values at or above the cutoff value for SUV_{max}, SUV_{mean}, WBMTV, and WBTLG, respectively ($P < 0.001$). DFS was 57.1 months, 59.2 months, 57.5 months, and 59.9 months in patients with low SUV_{max}, SUV_{mean}, WBMTV, and WBTLG, respectively [Figure 3].

Table 1: Patient characteristics

Patient characteristics	Value
Median age (range)	58 (22-82)
Sex	
Male	118
Female	35
Histology	
Adenocarcinoma	96
Squamous	44
Others	13
Stage	
I	42
II	76
III	35
Type of surgery	
Lobectomy	120
Bilobectomy	14
Pneumonectomy	17
Wedge resection	2
Neoadjuvant treatment	
Yes	32
No	121

Cox proportional hazards model was used in the multivariate analysis taking variables showing statistical significance in univariate analysis. Higher WBTLG (hazard ratio [HR] = 2.70, $P = 0.041$) and TNM staging (HR = 1.63, $P = 0.035$) were after adjustment for significant univariate variables for OS. For DFS, higher WBTLG (HR = 3.08, $P = 0.007$) was statistically significant after adjustment for TNM stage, sex, and adjuvant therapy. A summary of univariate and multivariate results for OS and DFS is shown in Table 2.

DISCUSSION

There is a high risk of disease recurrence and death following curative resection of early-stage NSCLC. Adjuvant therapy was recently explored to reduce recurrence and prolong survival by eliminating locoregional residual tumor cells and occult metastases, and is highly dependent on tumor staging. Even after stratifying patients with advanced molecular and pathological markers, survival rates remain unsatisfactory in similar patient groups. It is important to identify precise prognostic factors that can predict early recurrence and can be used to select patients for adjuvant therapy. With the widespread use of ^{18}F-FDG PET-CT in lung cancer, which can differentiate lesions with different biologic behaviors in addition to staging, its role in the prediction of local recurrence and survival must be investigated. Our study was performed with an aim to evaluate the prognostic value of different metabolic and volumetric parameters such as SUV_{max}, SUV_{mean}, WBMTV, and WBTLG obtained from the baseline ^{18}F-FDG PET-CT performed in surgically treated NSCLC patients.

In our study, we found that a higher WBTLG was significantly associated with an increased risk of recurrence and death independent of tumor staging and other significant prognostic factors. Other PET parameters such as SUV_{max}, SUV_{mean}, and WBMTV did not show any statistical significance after adjusting for the stage and other factors showing significance. Many recent studies have shown that whole-body tumor burden, best assessed with WBMTV and WBTLG, has significant prognostic value in patients with lung cancer independent of TNM stage and is superior to the conventional semiquantitative parameters such as SUV_{max} and SUV_{mean}.[12-16] Our results showed that WBTLG is superior to SUV_{max}, SUV_{mean}, and WBMTV in prognosticating the surgically resected NSCLC patients. Park *et al*. in a retrospective study found out that TLG has an independent prognostic value for OS.[15] Similarly, Chen *et al*. in a retrospective study of 105 patients evaluated the

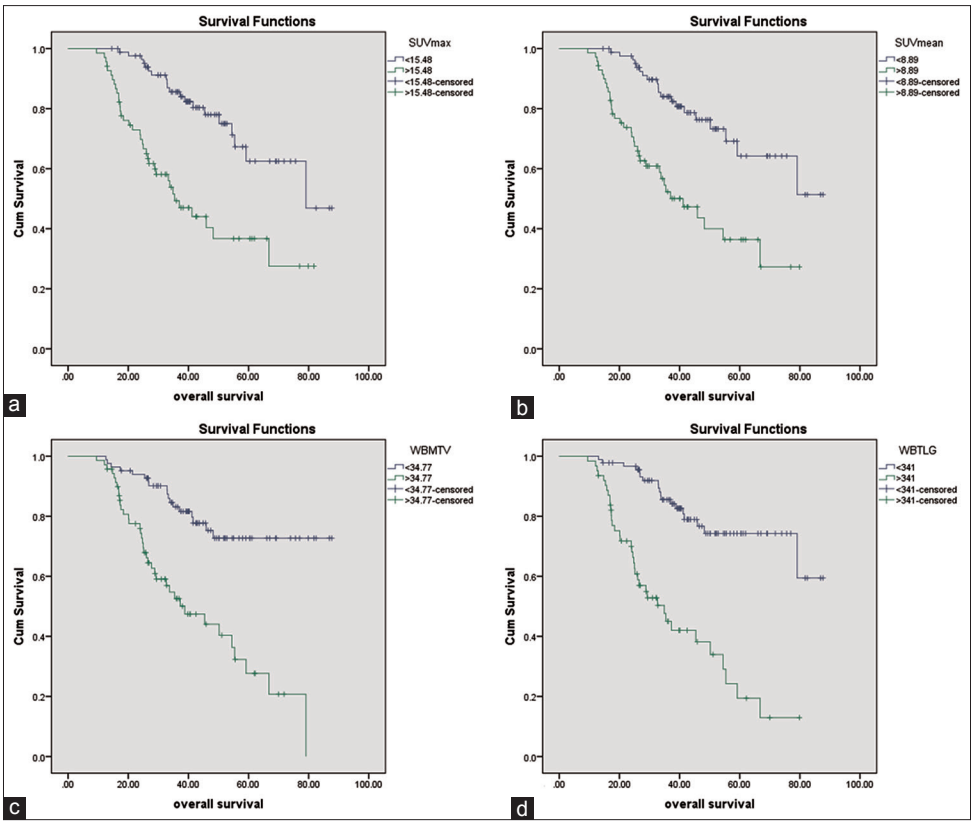


Figure 2: Kaplan–Meier curves of overall survival for standard uptake value max (a), standard uptake value mean (b), whole-body metabolic tumor volume (c), and whole-body total lesion glycolysis (d)

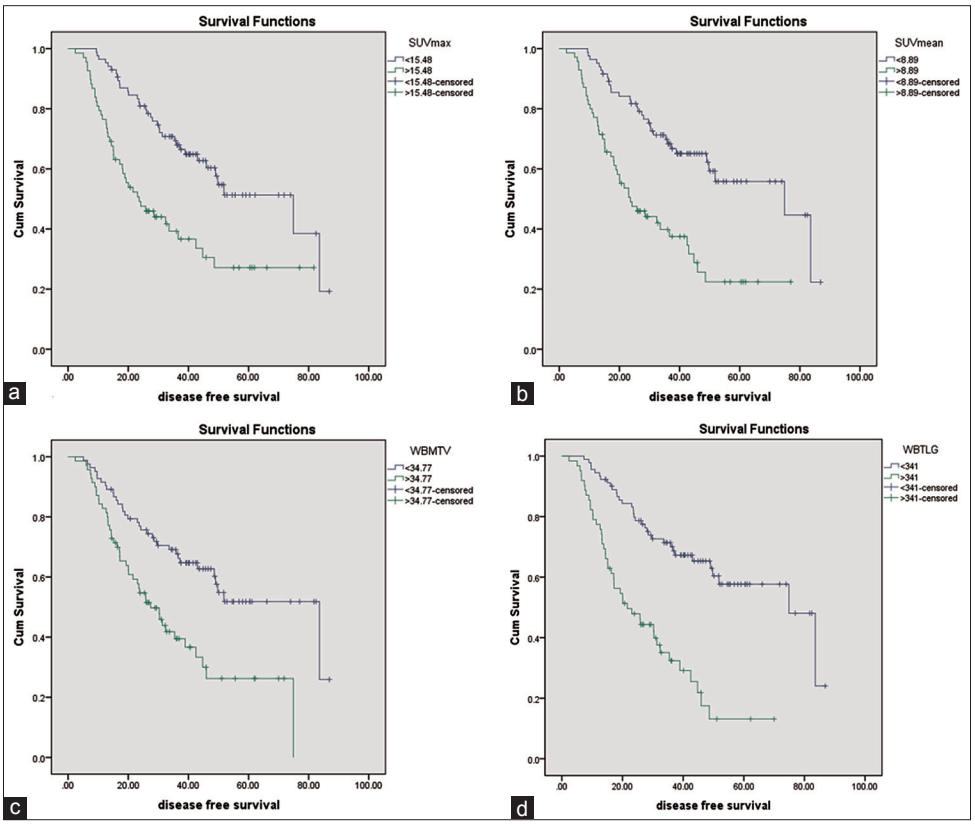


Figure 3: Kaplan–Meier curves of disease-free survival for standard uptake value max (a), standard uptake value mean (b), whole-body metabolic tumor volume (c), and whole-body total lesion glycolysis (d)

Table 2: Summary of univariate and multivariate analysis results for overall survival and disease-free survival

Variable	Overall survival (*P*)		Disease-free survival (*P*)	
	Univariate	Multivariate	Univariate	Multivariate
Median age (years)				
<58 versus ≥58	0.89	NA	0.39	NA
Histopathology adenocarcinoma versus others	0.84	NA	0.21	NA
Neoadjuvant treatment				
Yes versus no	0.92	NA	0.39	NA
Surgery				
Lobectomy versus pneumonectomy	0.83	NA	0.51	NA
Sex				
Male versus female	0.02	0.95	0.57	NA
Stage	0.001	0.035	0.006	0.07
Adjuvant treatment				
Yes versus No	0.002	0.79	0.008	0.55
SUV_{max}				
<15.48 versus ≥15.48	0.001	0.24	0.001	0.98
SUV_{mean}				
<8.89 versus ≥8.89	0.001	0.49	0.001	0.14
WBMTV				
<34.77 versus ≥34.77	0.001	0.38	0.001	0.75
WBTLG				
<341.1 versus ≥341.1	0.001	0.041	0.001	0.007

SUV_{max}: Maximum standardized uptake value; SUV_{mean}: Mean standardized uptake value; WBMTV: Whole-body metabolic tumor volume; WBTLG: Whole-body total lesion glycolysis; NA: Not applicable

value of volumetric parameters obtained from FDG PET-CT. In multivariate analysis, only TLG remained statistically significant among the PET parameters and proved to have independent prognostic value for survival.[11]

Early studies were showing the prognostic value of SUV, but SUV itself has several shortcomings. SUV_{max} reflects only the highly metabolically active focus and does not represent the true tumor burden or whole tumor. In addition, SUV depends on a variety of factors such as body weight, blood glucose, length of uptake period, type of scanner, and reconstruction techniques used. Finally, SUV_{max} does not take into account the size or volume of tissue which itself is a known prognostic marker. Because of these shortcomings, PET volumetric parameters such as MTV and TLG, which represent the entire tumor, were evaluated in clinical practice. Over that, MTV and TLG of multiple lesions can be summed up to derive WBMTV and WBTLG, which is an index of whole-body tumor burden. This is not possible with SUV and is a disadvantage when there are multiple lesions. In addition, these volumetric parameters seem superior to T staging, which considers only the longest dimension and does not represent the entire tumor. Whereas the volumetric assessment uses the three-dimensional geometry of the tumor and is more representative of the tumor morphology. MTV reflects the metabolically active tumor volume and can be easily calculated by different PET software. TLG is the product of MTV and SUV_{mean}. TLG combines the volumetric and metabolic information obtained from 18F-FDG PET-CT and reflects both the metabolic tumor volume and degree of metabolic activity. Hence, TLG seems to a better parameter to prognosticate patients. In our study also, WBTLG came out as the better parameter in patient prognostication.

Even though many studies have been done and shown the prognostic value of ^{18}F-FDG PET-CT in NSCLC, no consensus has been reached on the optimal cutoffs of the parameters to be taken for stratifying the patient groups. Different studies have come up with a range of cutoff values in different patient population. Liu *et al*. in a review article reported that the cutoff points ranged from 2.4 to 20 for SUV_{max}, 2.95 to 37.34 for MTV and TLG values ranged from 9.61 to 407.48.[17] The cutoff point used in our analysis was 15.48, 8.89, 34.77, and 341.1 for SUV_{max}, SUV_{mean}, WBMTV, and WBTLG, respectively. These cutoff values for metabolic parameters in our study were close to those obtained by Zhang *et al*. in a cohort of 104 surgically treated NSCLC patients.[14] There should be stage-specific cutoff values for different metabolic parameters for better risk stratification.

Therefore, the addition of tumor burden measurements can help further stratify patients within each stage and optimize treatment method. PET-based parameters such as WBTLG can provide a complete estimation of the true tumor volume and biological aggressiveness. WBTLG values can be used a quantitative prognostic factor independent of TNM

staging. Hence, surgical patients within the same stage can be stratified by using WBTLG into high risk and low risk for recurrence or death and can modify the treatment strategies accordingly. Incorporating metabolic tumor burden in trials could help identify high-risk patients who would most benefit from adjuvant or neoadjuvant therapies, improve patient selection by recruiting comparable risk patients, and produce more meaningful results. The inherent disadvantages of a single-center, retrospective observation study are the potential limitations. Prospective multicentric studies in a larger patient cohort are needed for the validation of these observations.

CONCLUSION

Whole-body tumor burden assessment with TLG has a significant prognostic value in patients with operated lung cancer. It is independent of stage and other clinical prognostic factors. WBTLG appears to a better prognostic parameter than other ^{18}F-FDG PET-CT-derived metabolic parameters such as SUV_{max}, SUV_{mean}, and WBMTV. Incorporation of TLG into clinical practice can further stratify patients within a stage and may be benefitted from additional therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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