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Clinical Significance of Quantitative FDG PET/CT Parameters in Non-Small Cell Lung Cancer Patients

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Background: An initial evaluation of non-small cell lung cancer (NSCLC) patients with 18F- fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan can modify treatment planning. We investigated the clinical significance of FDG PET/CT quantitative parameters (QPs) in NSCLC patients.

Materials and Methods: We included 125 NSCLC patients for initial staging FDG PET/CT scan. The primary tumor (T), regional lymph node metastases (N), and distant metastases (M) were evaluated on FDG PET/CT images. QPs, including standard uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were calculated separately for each T, N, and M lesion and also for the whole body. Statistical analysis through SPSS version 22 was used to evaluate the clinical significance of PET/CT QPs concerning primary tumor pathology characteristics, initial tumor stage, and patient's prognosis.

Results: We followed the patients for 19.28 (±11.42) months. Considering primary tumor pathology, there was a significant difference in FDG PET/CT QPs, including primary tumor SUVmax (p=0.00), metastases SUVmax (p=0.014), whole-body MTV (p=0.045), and whole-body TLG (p=0.002). There was also a significant difference in QPs, including primary tumor SUVmax (p=0.00) and regional lymph node metastases SUVmax (p=0.048) when accounting for tumor initial stage. There was a significant prognostic value for the whole-body TLG (p=0.01) and a cut-off point of 568 was reached to differentiate better versus worse survival outcome.

Conclusion: We demonstrated a statistically significant difference in FDG PET/CT QPs when accounting for primary NSCLC pathology characteristics and initial stage, as well as patient's prognosis, and recommend incorporating QP values into clinical PET/CT reports.

Key words: FDG PET/CT; Non-Small Cell Lung Cancer; Tumor Staging; Prognosis

INTRODUCTION

Lung cancer is the leading cause of cancer in males, comprising 17% of the total new cancer cases and 23% of the total cancer-related deaths (1).

Despite the success in the delineation of tobacco smoking as the major risk factor for lung cancer, this highly preventable disease remains among the most common and most lethal cancers globally. Novel approaches in the classification of lung cancer based on molecular techniques have started to bring new insights to its etiology, in particular among nonsmokers (2,3),

and despite advances in treatment modalities, the survival rate of lung cancer patients is still unfavorable (4).

Positron emission tomography (PET) is a non-invasive imaging modality with 18F- fluorodeoxyglucose (FDG) being the most commonly used radiotracer, acting as an analogue of glucose, which surrogates the rate of metabolic activity in different tissues (5). The rate of metabolic activities, including glycolysis and glucose uptake in malignant cells, is usually increased, causing increased FDG uptake on the PET images (6). Non-small cell lung cancer (NSCLC) initial staging is now a widely accepted indication for PET imaging (7).

Studies have demonstrated that using FDG PET/CT scan in patients with NSCLC is helpful for more precise initial staging and avoiding futile thoracotomies (8,9). FDG PET/CT scan is more accurate for detecting unexpected metastatic lesions in NSCLC patients than other imaging modalities (10,11).

Approximately 85% of all lung cancers are NSCLC with adenocarcinoma and squamous cell carcinoma being the most common subtypes. For inoperable NSCLC patients, radiotherapy and chemotherapy play a pivotal role in cancer control (2) and early prediction of the treatment response in these high-risk patients may result in timely therapeutic interventions, in which FDG PET/CT semi-quantitative parameters have demonstrated promising results (12).

To date, the most important, reliable, and standard semi-quantitative PET parameter used is the standardized uptake value (SUV), particularly (SUVmax). However; recent studies have shown that volumetric parameters measured on PET images may have significant prognostic value in patients with NSCLC. The most commonly used volumetric parameters in FDG PET scan surveys include metabolic tumor volume (MTV) and total lesion glycolysis (TLG). Higher values of MTV and TLG may be associated with a higher risk of poor prognosis and mortality in addition to more aggressive pathologic features, including a poor degree of cell differentiation and unfavorable type of tumor histology (13-15). The NSCLC lesions can be more accurately evaluated with the information obtained from the assessment of tumor metabolic activity and FDG PET/CT scan volumetric parameters may be used for the evaluation of response to the initial neoadjuvant therapy (16, 17).

The aim of this study was to investigate the relationship between FDG PET/CT scan semi-quantitative parameters, primary pathology of NSCLC, and patient's prognosis. According to the latest NCCN recommendations, performing FDG PET/CT for initial staging in the majority of patients with NSCLC is mandatory, which can significantly influence treatment planning (18-20).

MATERIALS AND METHODS

Study Protocol

In this cross-sectional study, we reviewed electronic medical records (EMR) of all patients in the cancer registry of Masih Daneshvari hospital, Tehran, Iran (1700 patients). We included all patients with NSCLC undergoing PET/CT imaging for initial tumor staging between January 2013 and December 2017 (125 patients).

We recorded all patient's demographic information, including age, gender, occupation, smoking status, other contributing risk factors, ultimate pathology diagnosis and its timing, initial PET/CT date, initial tumor stage, treatment methods, including surgery, radiotherapy, and chemotherapy with exact dates, including starting and finishing time and possible complications after treatment and stratified them according to the final pathology diagnosis, disease stage, treatments received risk factors, and survival outcomes. We retrieved FDG PET/CT images from the picture archiving and communication system (PACS) and reviewed them on a version 4.5 advantage workstation (ADW). For each patient, the primary tumor (T), regional lymph node metastases (N), and distant metastases (M) reevaluated jointly by an experienced nuclear medicine physician and a radiologist. Using the ADW 4.5 Workstation software, the

PET-related semi-quantitative parameters, including maximum standardized uptake value (SUVmax), MTV, and TLG parameters were calculated separately for each T, N, and M lesion. According to the PERCIST criteria (PET response criteria for solid tumors) (21), for each patient, the maximum of five lesions with the highest FDG absorption rates with a maximum of two lesions per organ was selected for quantitative evaluation.

Ethics

All Ethical issues, such as double submission, conflict of interest, co-authorship, etc. were considered carefully in this research. Ethical permission for the study was obtained from the ethics committees of Shahid Beheshti University of Medical Sciences and the participating hospital institutional review board (IRB) waived the patient's informed consent.

Semi-quantitative FDG PET/CT parameters definition

SUVmax: Maximum concentration of FDG in the addressed tumor (injected dose/body weight).

MTV: Metabolic tumor volume calculated by including any area of the tumor with FDG concentration equal or more the 41% (standard software cut-off point) of SUVmax in the region of interest (ROI).

TLG: Total lesion glycolysis calculated by multiplying MTV and SUVmean for each lesion Whole-body MTV: Sum of all calculated MTVs.

Whole-body TLG: Sum of all calculated TLGs.

Statistical Analysis

Data were analyzed using SPSS version 22 (SPSS Inc., Chicago, IL, U.S.A.) software. Results were presented descriptively as number (percentage) for categorical variables and as means and standard deviations (SD) or as medians and interquartile ranges (IQR) for continuous variables.

The obtained means of the two groups were compared with the Student's t-test and Mann-Whitney U test for multiple groups comparisons and also the one-way analysis of variance (ANOVA) or Kruskal-Wallis test (or median test) were used for parametric or non-parametric data, respectively. Differences between categorical variables were assessed using the Chi-square test and Fisher's exact test.

We presented survival as Kaplan-Meir survival curves with analysis performed using the Mantel-Cox log-rank test and Gehan–Breslow–Wilcoxon test. Cox univariate and multivariate analyses were performed to adjust for important prognostic factors.

All tests were bilateral and a value of 0.05 or less was our limit for statistical significance.

RESULTS

We included 125 NSCLC patients (92 males and 33 females) with a mean age of 60.67±11.18 (25-79) years.

Adenocarcinoma was the most common primary pathology (60%) followed by squamous cell carcinoma (SCC) (40%) in all cases.

Non-parametric median test demonstrated a significant difference in primary tumor SUVmax SUVmax- T (p=0.00), primary tumor TLG TLG-T (p=0.014), metastasis SUVmax-M (p=0.014), whole-body MTV (p=0.045) and whole-body TLG (p=0.002) when accounting for primary tumor pathology (Table 1).

Initial tumor staging data were collected from EMR and compared with PET scan quantitative parameters.

The 7th edition of the American Joint Committee on Cancer (AJCC) was used for staging purposes by the hospital cancer registry because a significant number of our patients had been referred prior to the 8th edition being clinically implicated in January 2018. According to the 7th edition tumor, node, metastasis (TNM) staging of NSCLC, the most common stage in our patients was stage IV. Distribution of patients in our study for different stages was as follows: 5 patients (4%) stage IA, 10 patients (8.0%) stage IB, 6 patients (4.8%) stage IIA, 7 patients (5.6%) stage IIB, 25 patients (20.0%) stage IIIA, 11 patients (8.8%) stage IIIB, and 61 patients (48.8%) stage IV.

The non-parametric median test demonstrated a significant difference in SUVmax- T (p=0.00) and also

regional lymph node metastasis (N) SUVmax SUVmax-N (p=0.048) when accounting for tumor initial stage.

The difference curve was more linear for lymph node (N) SUVmax comparing to the lymph node MTV (Figure 1).

Non-parametric Kruskal-Wallis test demonstrated a significant difference in primary tumor MTV (p=0.001) and TLG (p=0.01) and also lymph node (N) MTV (p=0.002) and TLG (p=0.003) when accounting for tumor initial stage. The difference was not significant for metastasis (M) MTV (p=0.112) and TLG (p=0.765). The difference was more linear for MTV and TLG values of lymph nodes compared with the primary tumor (Figure 2).

Evaluation of the metastases demonstrated 65 patients (52%) with no metastases. Most common metastases were in the thorax in 32 patients (25.6%), including contralateral lung, malignant pleural effusion, and metastatic pleural nodules. Single extrathoracic metastasis was observed in 16 patients (12.8%) and multi-organ metastasis was present in 12 patients (9.6%).

Non-parametric Mann-Withny U test demonstrated the significance of SUVmax- T (p=0.007), SUVmax-N (p=0.016), TLG (p=0.02), and whole-body MTV (p=0.031) to differentiate metastatic versus non-metastatic patients (Table 2).

Table 1. Correlation of FDG PET/CT semi-quantitative parameters with primary lung cancer pathology (statistically significant values are highlighted in yellow)

FDG PET semi- quantitative values	Adenocarcinoma		SCC[a]		P-value
	Number of patients	Median	Number of patients	Median	
Primary T[b] SUVmax	75	9.30	50	15.50	0.000
Primary T MTV[e]	75	28.56	50	42.35	0.093
Primary T TLG[f]	75	109.25	50	380.48	0.014
Lymph node met N[c] SUVmax	75	9.00	50	12.70	0.602
Lymph node met N MTV	75	13.04	50	13.66	0.784
Lymph node met N TLG	75	35.08	50	54.35	0.602
Metastasis M[d] SUVmax	75	7.40	50	14.85	0.014
Metastasis M MTV	75	9.51	50	7.82	0.107
Metastasis M TLG	75	31.88	50	36.73	0.405
Whole body MTV	75	41.10	50	59.43	0.045
Whole body TLG	75	205.14	50	489.90	0.002

[a] Squamous cell carcinoma; [b] Primary tumor; [c] Metastatic lymph node; [d] Distant metastasis; [e] Metabolic tumor volume; [f] Total lesion glycolysis

Table 2. Correlation of FDG PET/CT semi-quantitative parameters with metastatic versus non-metastatic NSCLC patients (statistically significant values are highlighted in yellow)

FDG PET semi- quantitative values	Metastatic Status						p-value
	Metastatic (thoracic + extra thoracic)			None			
	Number of patients	Mean Rank	Median	Number of patients	Mean Rank	Median	
Primary T SUVmax	60	51.43	12.00	65	68.43	15.55	0.007
Primary T MTV	60	63.32	36.28	65	56.73	31.69	0.298
Primary T TLG	60	60.36	252.77	65	59.65	215.25	0.911
Lymph node met N SUVmax	60	44.58	13.15	65	32.30	8.10	0.016
Lymph node met N MTV	60	41.16	14.50	65	38.61	11.44	0.623
Lymph node met N TLG	60	45.49	69.12	65	33.44	32.92	0.020
Whole body MTV	60	67.46	66.50	65	53.77	43.47	0.031
Whole body TLG	60	63.08	425.55	65	58.00	309.61	0.423

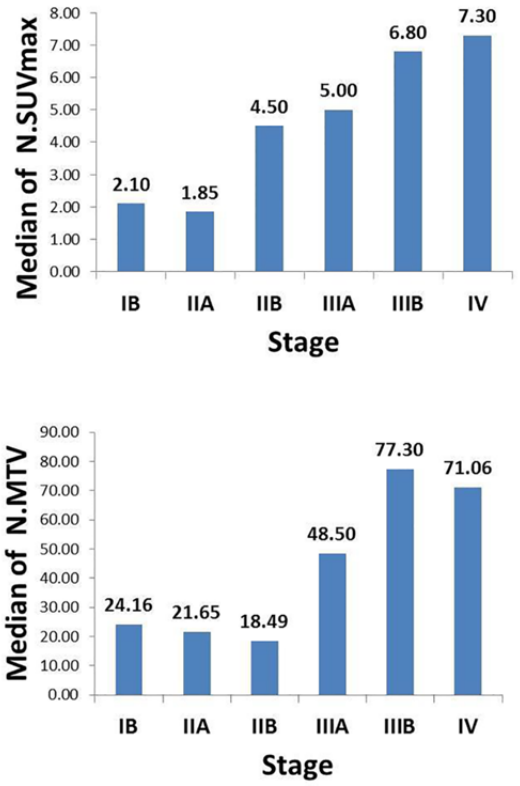

Figure 1. Significance of lymph node metastasis (N) SUVmax and MTV when accounting for primary lung cancer stage

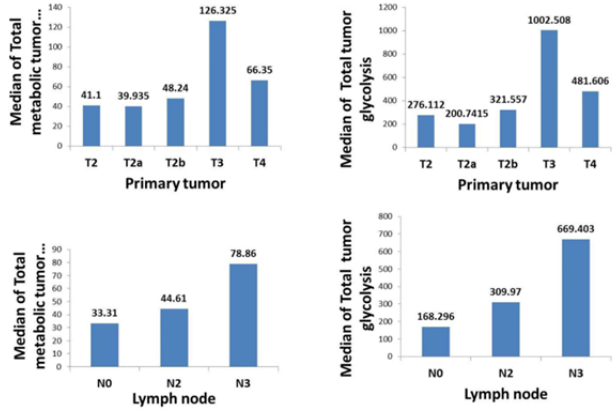

Figure 2. Significance of primary tumor (T) and lymph node metastasis (N) metabolic tumor volume and total lesion glycolysis when accounting for primary lung cancer stage

There was no statistically significant difference in quantitative FDG PET/CT parameters to differentiate between thoracic versus extra-thoracic ($0.099<p<0.844$) and also between uni-organ versus multi-organ ($0.197<p<0.897$) metastatic patients when p-values were individually calculated for each FDG PET/CT semi-quantitative parameter.

The patients were followed for 19.28±11.42 (0.7-61) months, from the date of the PET/CT scan to the patient's last follow-up or death. Survival rate was calculated from the date of initial diagnosis (recorded on EMR) to the last follow-up or death. The mean survival time was 18.46±10.5 (0.7-61.0) months in females and 21.59±13.6 (3.0-46) months in males, which was not significantly different ($p=0.12$).

At the end of the follow-up, 98 patients (78.4%) were alive with a mean survival rate of 21.50±11.98 (0.7-61) months and 27 patients (21.6%) died with a mean survival rate of 12.22±5.92 (1-24) months.

There was no statistically significant relationship between primary tumor pathology and patient's survival ($p=0.335$). Also, There was no statistically significant relationship between primary tumor stage and patient's survival ($p=0.062$).

Among FDG PET/CT scan semi-quantitative parameters, there was no statistically significant difference in the primary tumor ($p=0.367$), lymph node ($p=0.876$), and also metastasis ($p=0.830$) semi-quantitative parameters when accounting for patient's survival.

The only semi-quantitative parameter with a significant relationship with the patient's survival was the whole-body TLG ($p=0.01$) demonstrating a longer survival rate in NSCLC patients with lower whole-body TLG at the initial staging PET/CT scan. We reached a cut-off point of 568.1 to differentiate between statistically significantly better or worse survival (Figures 3 and 4).

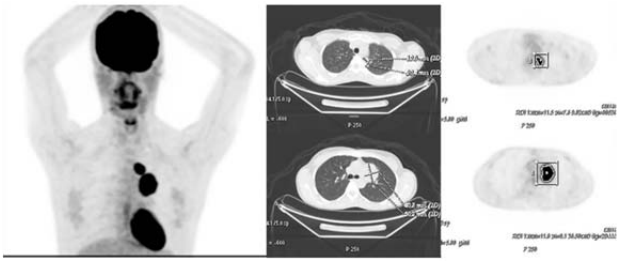

Figure 3. NSCLC (invasive adenocarcinoma) in left upper lobe with ipsilateral mediastinal massive lymphadenopathy. Whole body TLG is equal to 312.8 with overall survival of 36 months toward the last follow-up.

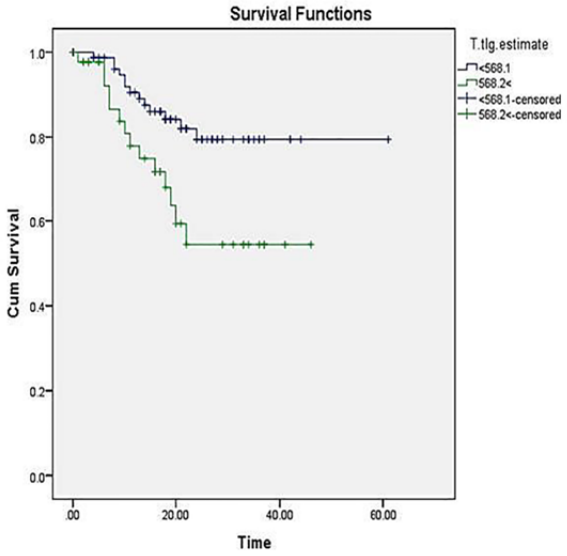

Figure 4. Significantly different survival between the two groups with total TLG fewer and more than the cut point of 581.

DISCUSSION

This cross-sectional study demonstrated that among all pathological features of NSCLC, the increase in whole-body TLG to more than the cut-off point of 568 is significantly associated with a decreased survival rate. Also, there was a significant correlation with the value of other semi-quantitative FDG PET/CT parameters with primary tumor pathology and also initial NSCLC stage as discussed in the results.

TLG value is representative of the metabolic activity in the entire neoplastic lesion and volumetric parameters, such as MTV and TLG can more accurately reflect the metabolic burden of neoplastic lesions to predict patients' prognosis. Several prognostic factors for predicting recurrence of cancer have been suggested, including primary tumor size, lymph node metastasis, and degree of tumor differentiation (21, 22).

Clinical staging plays an important role in predicting survival and can influence management planning in lung cancer patients. Since its introduction in the 1970s, the TNM staging has undergone significant revisions with the latest 8th edition being effective internationally from January 2018.

CT scan-based tumor volume may not represent actual tumor size or tumor burden because tumors are not always uniformly shaped and could contain necrotic portions with nonviable tissues. Post-obstructive collapsed consolidation may also be difficult to differentiate from an actual tumor based on CT images.

Functional imaging provides metabolic and volumetric information, and more accurately reflects the actual tumor burden. Even in small cell lung cancers, gross tumor volume determined by FDG PET/CT scan as part of radiation treatment planning and TLG (product of MTV and SUV mean) may predict prognosis (23-25).

A few studies have considered the correlation between semi-quantitative FDG PET/CT parameters and primary tumor pathology and prognosis in patients with NSCLC. Liao et al. evaluated the prognostic value of the metabolic tumor burden in nonsurgical patients with NSCLC and concluded that FDG PET/CT semi-quantitative parameters are prognostic measures independent of the clinical stage with low interobserver variability and may be used to further stratify nonsurgical patients with NSCLC. They suggested that MTV and TLG are better prognostic measures than SUVmax and SUVmean (26). Zaizen et al. also evaluated the prognostic significance of TLG in patients with advanced NSCLC after chemotherapy and concluded that TLG may be more useful than SUVmean and SUVmax for predicting progression-free survival and overall survival in NSCLC patients and suggested routine TLG measurement on FDG-PET imaging in advanced NSCLC patients (27). Park et al. also demonstrated the significant prognostic value of TLG for overall survival prediction in patients with stage IA NSCLC (28).

In a study similar to ours, Chen et al. investigated the prognostic value of whole-body TLG at pretreatment FDG PET/CT in NSCLC patients. They concluded that the whole-body TLG is of prognostic value for NSCLC and may be a promising tool for stratifying patients with NSCLC for risk-adapted therapies. Interestingly, they reached the cut-off point of 655 for TLG to differentiate one-year progression-free survival, which is close to the

cut-off point of 568 in our study to differentiate better than worse overall survival (29).

In our study, we were able to separate NSCLC patients for better or worse overall survival time based on the calculated whole-body TLG value, and due to the relatively small number of our patients and also limited follow-up data in our EMR system, we were not able to evaluate progression- free survival time as Chen et al. performed.

We also did not find a statistically significant relationship between overall survival time and other volumetric FDG PET/CT semi-quantitative parameters, such as a primary tumor, metastatic regional lymph node, and distant metastasis based on SUVmax, MTV, or TLG value.

As we discussed earlier, our results demonstrated a statistically significant relationship between SUVmax-T, TLG-T, SUVmax-M and also whole-body MTV/TLG values with primary tumor pathology. However; SCC lung cancer patients had significantly higher values than adenocarcinoma patients. SUVmax-T, SUVmax-N, and TLG and also the whole-body MTV were also significantly different between metastatic and non-metastatic patients, with higher values calculated in metastatic patients.

The prognostic value of FDG PET/CT semi-quantitative parameters has also been evaluated in other types of cancers, such as pharyngeal carcinoma, esophageal cancer, and non-Hodgkin lymphoma with promising results (30-32).

Although it is a promising result, the volume-based FDG PET semi-quantitative parameters (especially for whole-body) need to be standardized in the measurement before they can be included in the medical report, in order to avoid confusion. At present, the most important, reliable, and standardized PET semi-quantitative parameter used is still SUV (particularly SUVmax). Although the newest volume-based PET parameters (MTV and TLG) are emerging, SUV remains an irreplaceable cornerstone for PET studies.

CONCLUSION

Whole-body TLG may predict patients' prognosis and overall survival time. Additionally, other FDG PET/CT semi-quantitative parameters are correlated with NSCLC pathology and initial stage. FDG PET/CT semi-quantitative parameters need to be standardized in the measurement before they can be included in the medical report.

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Conflict of Interest

Authors of this manuscript declare that there is no funding or conflict of interest for this work.

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