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Prognostic Value of ^{18}F-FDG PET/CT Metabolic Parameters in Surgically Treated Stage I Lung Adenocarcinoma Patients

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Purpose of the Report: This article aims to explore the prognostic role of ^{18}F-FDG PET/CT metabolic parameters in stage I lung adenocarcinoma patients.

Patients and Methods: One hundred eighty pathological stage I lung adenocarcinoma patients were retrospectively reviewed. Semiquantitative analysis of FDG tumor uptake was performed with TrueD software on the Siemens Leonardo workstation. SUV_{mean} and MTV were calculated using SUV threshold of 41% of SUV_{max}; the total lesion glycolysis (TLG) was calculated as the product of SUV_{mean} and MTV. Correlation was evaluated using Spearman correlation coefficient. Maximally selected rank statistics was performed to detect the optimal cutoff used for dichotomizing each PET parameter (6.5 for SUV_{mean}, 9.6 for SUV_{max}, and 19.1 for TLG).

Results: Our main finding was the significant correlation between ^{18}F-FDG PET/CT parameters (SUV_{mean}, SUV_{max}, and TLG) and disease-free survival in pathologic stage I non–small cell lung cancer. SUV_{mean} has the greatest accuracy in recurrence prediction (integrated area under the curve, 0.803; 95% confidence interval, 0.689–0.918). We run the maximally selected rank statistics to provide the classification of observations in 2 groups by a continuous predictor parameter; the free from recurrence rate was significantly greater in patients with $SUV_{mean} \leq 6.5$, $SUV_{max} \leq 9.6$, and TLG ≤19.1.

Conclusions: Our research supports the hypothesis that SUV_{mean}, SUV_{max}, and TLG are well correlated with free from recurrence rate in stage I adenocarcinoma patients, subjected to pulmonary lobectomy. Our findings also indicate these markers as promising prognostic indicators.

Key Words: PET/CT, metabolic parameters, prognostic value, lung adenocarcinoma, pulmonary lobectomy

(*Clin Nucl Med* 2021;46: 621–626)

Lung cancer is the most common form of tumor and is the leading cause of cancer-related mortality worldwide. Tumor node metastasis stage seems to be the main prognostic factor, yet the biological heterogeneity of lung cancer subtypes limits its prognostic value as well as its role in treatment planning.[1] In the last decade, PET/CT with ^{18}F-FDG has demonstrated its high prognostic value for cancer staging, monitoring of treatment response, and prognosis prediction for non–small cell lung cancer (NSCLC).[2] SUV is a semiquantitative determination of the normalized concentration of radioactivity. SUV is measured over a region of interest as the ratio of tissue radioactivity concentration and the injected dose adjusted by body weight, with SUV_{max} as its maximum pixel value, representing the most metabolically active part of the tumor. The SUV_{mean} is the mean value of metabolic activity in a chosen region, whereas the peak SUV (SUV_{peak}), the average value within a small, fixed region of interest in the tumor, is considered a robust alternative to SUV_{max}.[3]

As a diagnostic parameter, SUV may be affected by biological and technological factors,[4] including technical errors in PET/CT examination procedures, such as accuracy of activity calibrators, clock synchronization, and postinjection time discrepancies. However, SUV is a highly repeatable imaging biomarker when acquired thoroughly after the PET/CT protocol.[5]

Compared with SUV_{mean}, SUV_{max} is not affected by the shape and size of volume of interest (VOI) and presents excellent interobserver repeatability.[4]

In an attempt to increase the clinical value of the SUV, volume-based parameters have been evaluated to measure metabolic activity in the whole tumor mass, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG). MTV is defined as the volume of tumors with increased glycolytic activity and is calculated according to attenuation-corrected ^{18}F-FDG PET images. TLG results from the product of SUV and lesion volume. MTV and TLG are useful indexes of tumor burden and aggressiveness, and they are promising tools for cancer prognosis and treatment response monitoring in oncologic patients.[3,6,7] Recent studies have shown that the ^{18}F-FDG PET/CT-normalized parameter (SUV_{max}) and the volume-based values (MTV and TLG) are potential prognostic factors for tumor aggressiveness[8] and patients' survival.[9,10] Among thousands of studies published to date on different types of cancers, there are only a few studies on NSCLC.[11] To broaden current knowledge on the prognostic value of SUV_{max}, TLG, and MTV in NSCLC, we reviewed all clinical reports of pathological stage I lung adenocarcinoma patients who underwent pulmonary lobectomy at two university hospitals in Northern Italy.

PATIENTS AND METHODS

This is an observational, cohort, bicentric single-arm retrospective study on lung adenocarcinoma patients who underwent pulmonary lobectomy between January 1, 2010, and December 31, 2018. Disease-free survival (DFS) was the primary clinical end point. We hypothesized an association between PET markers and the free from recurrence (FFR) rate. Inclusion criteria were

Received for publication January 29, 2021; revision accepted March 29, 2021.
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Conflicts of interest and sources of founding: none declared.
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
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ISSN: 0363-9762/21/4608–0621
DOI: 10.1097/RLU.0000000000003714

TABLE 1. Demographic and Preoperative Characteristics of Patients

	No Recurrence	Recurrence	*P*
Age, median (IQR), y	71 (12)	69 (15)	0.398
Sex, female, n (%)	62 (40.3)	11 (39.3)	0.999
Stage, n (%)	17 (11.0)		
IA1	17 (11.0)	1 (4.6)	0.382
IA2	49 (31.8)	6 (21.4)	0.380
IA3	33 (21.4)	11 (39.3)	0.073
IB	55 (35.7)	10 (35.7)	0.999
Tumor size, median (IQR), mm	20.0 (11.8)	22.0 (11.3)	0.070
SUV_{mean}, median (IQR)	2.6 (3.4)	4.4 (4.8)	0.003
SUV_{max}, median (IQR)	4.6 (5.9)	8.2 (7.8)	0.002
MTV, median (IQR), cm^3	5.3 (7.1)	5.1 (5.6)	0.952
TLG, median (IQR)	13.5 (22.7)	22.0 (23.0)	0.035
No. resected lymph nodes, median (IQR)	6 (4)	7 (4)	0.750

patients diagnosed with pathological stage I lung adenocarcinoma (VIII tumor node metastasis edition), who underwent lobectomy and hilar-mediastinal lymphadenectomy, and those older than 18 years. Exclusion criteria included induction chemotherapy, adjuvant chemotherapy or radiotherapy, surgical resection other than pulmonary lobectomy, type 1 diabetes, histotype different from adenocarcinoma, and previous tumor in the last 5 years. All recruited patients underwent surgery at the Division of Thoracic Surgery and Lung Transplantation at the IRCCS Ca' Granda Ospedale Maggiore Policlinico Foundation in Milan, and the Division of Thoracic Surgery at Ospedale di Circolo Fondazione Macchi in Varese. Patients underwent preoperative scans with ^{18}F-FDG PET at the Nuclear Medicine of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan and Nuclear Medicine of Ospedale di Circolo Fondazione Macchi in Varese. Patient preparation, FDG preparation, and the imaging procedure were identical at both institutions. The PET/CT scanner (Biograph TruePoint; Siemens Medical solutions, Erlangen, Germany) and the workstation software for image analysis (TrueD Image Analysis; Siemens Medical Solutions, Erlangen, Germany) were the same for both centers. All patients were fasting for at least 6 hours before PET/CT examination. Whole-body image acquisition was performed 60 minutes after IV injection of ^{18}F-FDG mean activity of 3.7 MBq/kg. For each patient, PET/CT scan was preceded by the acquisition of a CT scout or topogram to define the field of view. Subsequently, a low-dose CT scan (120 kV and 90 mAs) was performed with automatic exposure control to correct the attenuation of PET images and for the anatomical localization of PET findings. PET/CT scan was acquired with a duration time of 3 minutes per bed, using the same axial field as the CT scan. PET data were corrected for attenuation and scattering, and then reconstructed on a 128 × 128-pixel matrix (pixel size, 1.3 × 1.3 mm^2) using iterative reconstruction algorithms (AW-OSEM, 2 iterations, 8 subsets). All PET/CT studies were reviewed by 2 nuclear medicine physicians with 20 years of experience, who were blinded to the clinical data. Semiquantitative analysis of FDG tumor uptake was performed with TrueD software on the Siemens Leonardo workstation (Siemens Healthcare, Erlangen, Germany). Contouring margins were automatically derived by applying a VOI at lung lesion on each PET/CT study, and the 3 sectional images (axial, sagittal, and coronal) were used to ensure accurate inclusion of the whole tumor and exclusion of adjacent normal structures. The SUV_{max} represents the most intense area (ie, voxel) of FDG uptake in a VOI. SUV_{mean} and MTV were calculated using an SUV threshold of 41% of SUV_{max}. TLG was calculated as the product of SUV_{mean} and MTV.

Pulmonary lobectomies were performed with radical intent; negative surgical margins were verified intraoperatively; hilar and mediastinal lymph node dissection was routinely performed. Pulmonary lobectomies were mainly carried out by video-assisted thoracic surgery, as this approach has been introduced in the 2 centers since 2011. Patients' follow-up was based on a systematic postoperative surveillance protocol using CT and chest x-ray over a 5-year

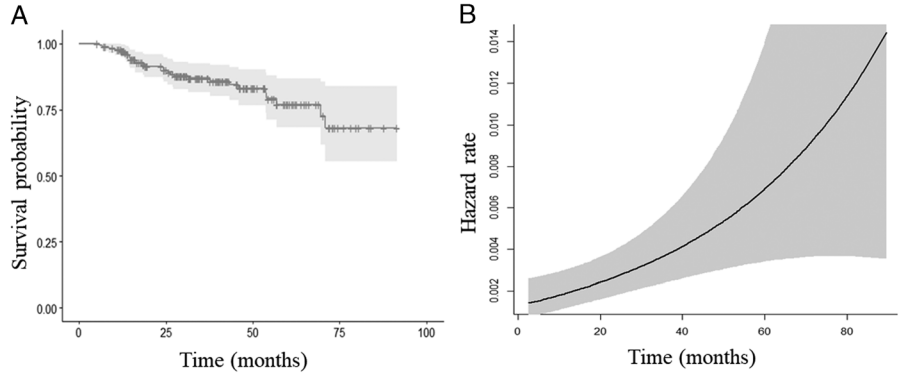

FIGURE 1. Kaplan-Meier curve of the time to recurrence (FFR time); time is expressed in months. **A,** Nonparametric adjusted hazards function and 95% CI (gray) relative to recurrence in the total cohort of patients (**B**).

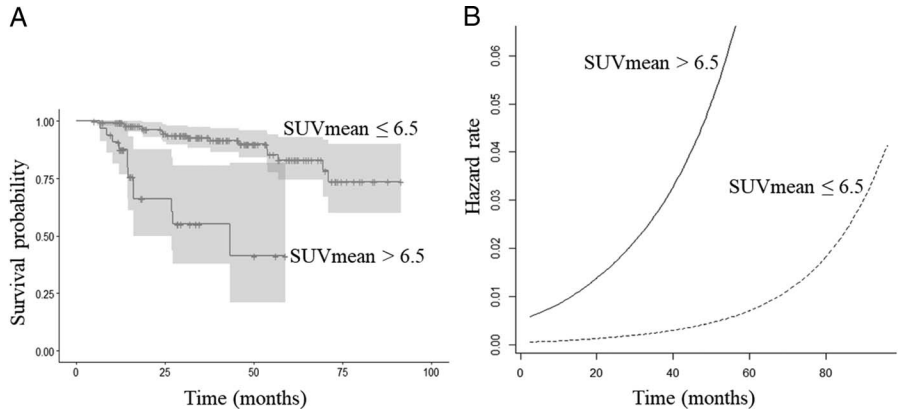

FIGURE 2. Kaplan-Meier survival curves for FFR by SUV_{mean}. Patients with SUV_{mean} ≤6.5 are labeled as "low"; patients with SUV_{mean} of >6.5 are labeled as "high" (**A**); the nonparametric adjusted hazards function relative to recurrence in patients with SUV_{mean} of ≤6.5 (dashed line) and with SUV_{mean} of >6.5 (continuous line) (**B**).

period. Additional CT or MRI was routinely performed if extrapulmonary metastases were suspected. For each patient, we collected demographic characteristics, medical history, pathologic data, and follow-up in an anonymized database. The study protocol was approved by the Clinical Research Ethics Committee of Milan, Area 2 (407_2019bis).

Statistical Analysis

Continuous data were presented as median and interquartile range (IQR). Categorical variables were shown as absolute and percentage frequencies. Either the signed rank test or χ^2 test was performed. Correlation was evaluated using Spearman correlation coefficient. Time-to-event data were displayed using the nonparametric Kaplan-Meier estimator. Maximally selected rank (MSR) statistics was performed to detect the optimal cutoff used for dichotomizing each PET parameter.[12,13] The hazards ratio was computed using the univariable or multivariable Cox regression model with Breslow approximation; the robust sandwich variance estimator was adopted to account for correlated groups of observations given by the multicentric nature of the data. The proportional hazards assumption was checked using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. To detect nonlinearity in the relationship between the log hazards and the covariates, we plotted the Martingale residuals against continuous covariates, inspecting the functional form. Influential observations were checked by graphical inspection of deviance residuals. To evaluate the predictive performance of PET parameters, we computed the time-dependent cumulative case/dynamic receiver operating characteristic (ROC) curve for censored survival data and the area under the ROC curve (AUC). In addition, we calculated the integrated area under the curve (IAUC) from the results of time-dependent ROC curves at some points in time.[14,15] Comparisons between the time-dependent ROC curves were made.[16]

The adjusted smooth hazards function was estimated nonparametrically by using B-splines collected from the perspective of generalized linear mixed models.[17] We also presented the restricted mean survival time (RMST) curves that reflect the mean FFR time for a patient with a certain value of a PET parameter.[18]

Confidence intervals were computed at 95%, and side *P* values were considered significant when less than 0.05. In all graphs, time value was expressed in months. All analyses were carried out using R-Cran software, version 3.5.3.[19]

RESULTS

During the recruitment phase, from January 1, 2010, to October 31, 2018, a total of 1204 patients underwent lobectomy in the 2 centers. Of these, 182 patients met the inclusion criteria and were included

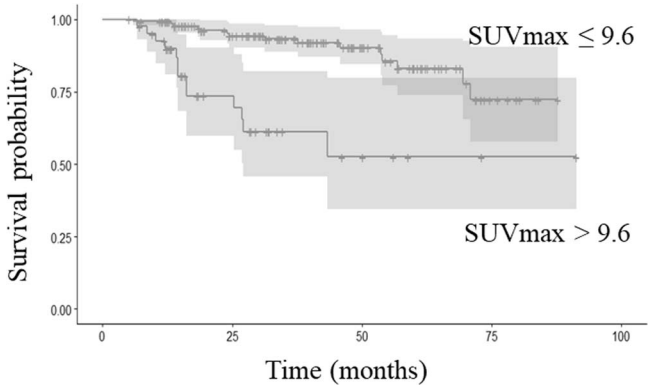

FIGURE 3. Kaplan-Meier survival curves for FFR by SUV_{max}. Patients with SUV_{max} of ≤9.6 are labeled as "low"; patients with SUV_{max} of >9.6 are labeled as "high."

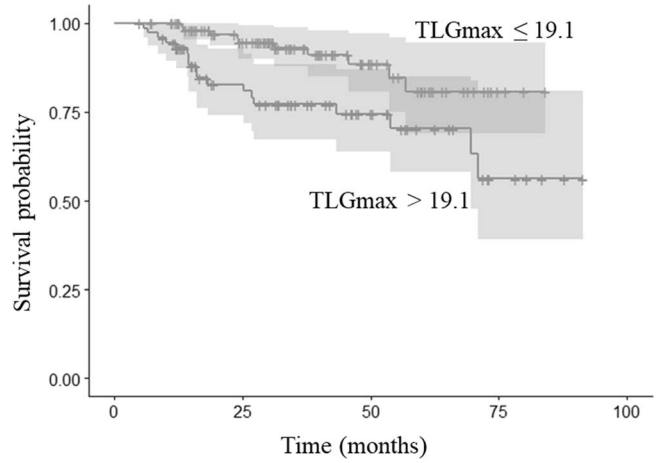

FIGURE 4. Kaplan-Meier survival curves for FFR by TLG. Patients with TLG ≤19.1 are labeled as "low"; patients with TLG >19.1 are labeled as "high."

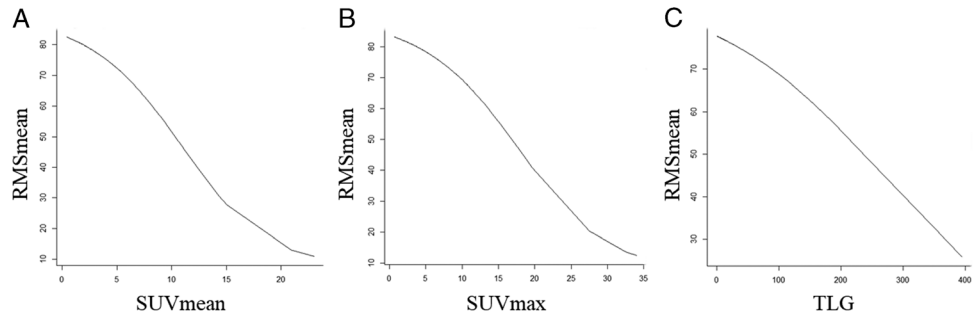

FIGURE 5. The RMST curve for SUV_{mean} (**A**), SUV_{max} (**B**), and TLG (**C**). The *y* axis shows the expected survival in months; the *x* axis shows the values of the PET biomarker.

in the study. There was no intraoperative or 30-day postoperative mortality in the selected cohort. None of the patients received adjuvant therapy. The median follow-up was 35 months (IQR, 32.5). The total number of recurrences was 28 (15.4%). Demographic and preoperative characteristics of the patients divided by recurrence status were summarized in Table 1. We found statistical association between SUV_{mean}, SUV_{max}, TLG, and cancer recurrence. In particular, SUV_{mean}, SUV_{max}, and TLG were approximately 40% higher in patients with recurrence than in patients without recurrence.

SUV_{max} had strong positive correlation with SUV_{mean} (Spearman $\sigma = 0.99$; 95% confidence interval [CI], 0.98–1.00), moderate positive correlation with TLG (Spearman $\sigma = 0.58$; 95% CI, 0.47–0.69), and weak negative correlation with MTV (Spearman $\sigma = -0.14$; 95% CI, −0.3 to −0.01).

The overall estimated 3-year and 5-year FFR rates were 0.87 (95% CI, 0.81–0.93) and 0.77 (95% CI, 0.69–0.87), respectively (Fig. 1A); Figure 1B shows the overall adjusted hazards function relative to recurrence.

The MSR statistic for SUV_{mean} values identified 6.5 as the optimal cutoff for dichotomizing patients' cohort in low SUV_{mean} subgroup ($SUV_{mean} \leq 6.5$; 149 patients) and high SUV_{mean} subgroup ($SUV_{mean} > 6.5$; 33 patients). The estimated 5-year FFR rate was 0.83 (95% CI, 0.74–0.93) and 0.44 (95% CI, 0.21–0.82) for the low SUV_{mean} subgroup and the high SUV_{mean} subgroup, respectively ($P < 0.001$) (Fig. 2A); Figure 2B depicts the adjusted hazards function relative to recurrence in SUV_{mean} groups.

SUV_{max} values were dichotomized at 9.6 by MSR statistic: low SUV_{max} subgroup ($SUV_{max} \leq 9.6$) included 141 patients, whereas 41 patients entered the high SUV_{max} subgroup. The estimated 5-year FFR rate was 0.82 (95% CI, 0.73–0.94) and 0.52 (95% CI, 0.35–0.80) for low SUV_{max} subgroup and high SUV_{max} group, respectively ($P < 0.001$) (Fig. 3).

The MSR statistic for TLG values dichotomized the patients' cohort at 19.1: low TLG subgroup and high TLG subgroup included 109 and 73 patients, respectively. The estimated 5-year FFR rate was 0.81 (95% CI, 0.69–0.94) for the low TLG subgroup (TLG ≤19.1) and 0.70 (95% CI, 0.58–0.85) for the high TLG subgroup ($P = 0.053$) (Fig. 4).

The RMST curves for SUV_{mean}, SUV_{max}, and TLG at 60 months are displayed in Figure 5, which shows the influence of these continuous biomarkers on FFR time.

In the univariable Cox regression analysis, SUV_{mean}, SUV_{max}, and TLG were statistically significant and proved associated with recurrence (Table 2). The multivariable analysis showed similar results (Table 3).

The SUV_{max} and SUV_{mean} showed similar performance ($P > 0.1$ for all follow-up time points) in light of their strong correlation, whereas SUV_{max} and SUV_{mean} were strongly different in terms of statistics from TLG ($P < 0.05$ for some follow-up time points > 10.5 months) in predicting the risk of recurrence.

The SUV_{mean} showed greatest accuracy in recurrence prediction (IAUC, 0.803; 95% CI, 0.689–0.918), followed by the SUV_{max} (IAUC, 0.794; 95% CI, 0.676–0.910) and TLG (IAUC, 0.650; 95% CI, 0.495–0.805).

Table 4A shows the predictive accuracy measures of SUV_{mean} over time at cut point of 6.5; Table 4B shows the predictive accuracy measures of SUV_{max} over time at cut point of 9.6.

DISCUSSION

The main finding of our retrospective study was the significant correlation between ^{18}F-FDG PET/CT parameters (SUV_{mean}, SUV_{max}, and TLG) and DFS in pathological stage I adenocarcinoma patients who underwent pulmonary lobectomy. SUV_{mean} had the greatest accuracy in recurrence prediction, followed by the SUV_{max} and TLG. Considering that threshold values are highly valued in the clinical setting, we run the MSR statistics, a widely accepted method to provide the classification of observations into 2 groups by a

TABLE 2. Univariable Cox Regression Analysis for Recurrence

Variable	Reference Category	Hazards Ratio (95% CI)	*P*
Sex	Female	1.18 (0.57–2.47)	0.656
Smoking history	No	1.53 (1.69–3.37)	0.293
Tumor size, mm		1.03 (0.99–1.07)	0.163
SUV_{mean} (categorical)	≤6.5	10.8 (4.80–24.53)	<0.001
SUV_{mean} (continuous)		1.29 (1.21–1.37)	<0.001
SUV_{max} (categorical)	≤9.6	5.02 (2.35–10.74)	<0.001
SUV_{max} (continuous)		1.14 (1.09–1.20)	<0.001
TLG (categorical)	≤19.1	2.22 (0.98–4.99)	0.0535
TLG (continuous)		1.006 (1.004–1.009)	<0.001
MTV (continuous)		0.98 (0.92–1.06)	0.642

TABLE 3. Multivariate Cox Regression for Recurrence

Variable	Hazards Ratio (95% CI)	*P*
SUV_{mean}	19.67 (7.88–49.11)	<0.001
SUV_{mean} (continuous)	1.34 (1.23–1.48)	<0.001
SUV_{max} (continuous)	1.16 (1.10–1.22)	<0.001
SUV_{max}	4.89 (1.17–20.42)	0.029
TLG	3.5 (1.38–8.9)	0.008
TLG (continuous)	1.007 (1.004–1.011)	<0.001
MTV (continuous)	0.97 (0.89–1.060)	0.510

TABLE 4. Predictive Accuracy Measure of SUV_{mean} Over Time at Cutoff Point of 6.5 (A) and SUV_{max} at Cutoff Point of 9.6 (B)

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
A. SUV_{mean}				
T = 16	69.9	88.3	27.1	97.9
T = 24	63.4	89.8	36.7	96.3
T = 34	52.8	93.4	54.7	92.9
T = 48	48.7	94.6	64.5	90.1
T = 57	39.5	97.3	79.4	85.9
B. SUV_{max}				
T = 16	69.9	84.1	21.6	97.8
T = 24	63.4	85.8	29.5	96.2
T = 34	58.5	91.2	50	93.6
T = 48	53.1	90.9	54.3	90.5
T = 57	43	91.9	58.3	86

continuous predictor parameter. The FFR rate was significantly greater in patients with SUV_{mean} ≤6.5, SUV_{max} ≤9.6, and TLG ≤19.1.

The prognostic/predictive role of ^{18}F-FDG PET/CT metabolic parameters in several malignancies has been broadly investigated. Vansteenkiste and collaborators published in 2004 a comprehensive literature review on the prognostic value of ^{18}F-FDG PET/CT in lung cancer patients; the authors hypothesized that the proliferative capacity of neoplastic cells, which is clearly associated with the ^{18}F-FGD uptake, could be related to prognosis. Five retrospective studies found a correlation between overall survival and SUV_{max}, even though a remarkable point was the very variable SUV_{max} threshold of these studies ranging from 5 to 20. Vansteenkiste et al also reported the multivariate survival analyses performed in the 4 studies; these studies identified SUV_{max} as an independent prognostic factor among other relevant covariates including cancer stage.[20] More recently, researchers from the University of Pennsylvania have published a narrative review on FDG activity as a prognostic indicator in patients with NSCLC. The authors reported the results from 4 studies that significantly correlated recurrence rate and time to recurrence with preoperative SUV_{max}. Moreover, the authors referred to 2 articles that analyzed volume-based ^{18}F-FDG PET/CT parameters; these studies found that MTV and TLG were independent predictors of poor disease-free and overall survivals.[21] Chinese researchers approached the topic more systematically by publishing a meta-analysis in 2016. This meta-analysis included 36 studies and 5807 patients. The adjusted hazards ratios for DFS were 2.43, 2.49, and 2.97 for SUV_{max}, MTV, and TLG, respectively. This meta-analysis also highlighted that the patients' heterogeneity, cancer stage miscellanea, retrospective cohorts, inhomogeneous PET/CT acquisition, and calculations protocols limited the application of PET/CT parameters as prognostic markers.[7] Our study tried to overcome these limitations with strict patient selection and identical acquisition protocols used in the 2 participating centers.

A recently developed method for the identification of imaging biomarkers is the radiomic analysis, a methodology that extracts a large number of quantitative features using mathematical models.[22] Ahn and collaborators studied 5 different machine-learning algorithms to investigate the prognostic value of PET-based radiomic features in 93 patients with stage I to III NSCLC who underwent radical surgery. The authors concluded that patients with poor DFS had tumors showing low contrast and high busyness texture features; random forest classifier was the machine learning approach with the best performance in predicting the recurrence risk.[23]

Pending the validation and dissemination of these latest modern imaging analysis methodologies, our study adds to the accumulating evidence that PET/CT parameters, such as SUV_{mean}, SUV_{max}, and TLG, are current and accessible predictors of NSCLC recurrence after curative surgery.

The present study has several limitations. First of all, this is a retrospective study. Nevertheless, one should bear in mind that the research subject is an extremely common pathology, and the primary object of the study (FFR rate) is the main purpose of the checks carried out on the operated patients. It is, therefore, logical to expect the loss to follow-up negligible. In fact, all selected patients underwent complete and accurate follow-up. Second, we admit that our patient cohort is not particularly numerous; on the other hand, by looking at previous articles published on this issue, our study is positioned in the range of those with the largest cohort. Because our analysis was performed on early-stage adenocarcinomas, we do not have data on the original mutational state. Therefore, we did not capture the possible impact of the mutational state on PET/CT parameters and recurrence rate; however, it is interesting to point out that some researchers find a correlation between low SUV_{max} and positive *EGFR* mutation in advanced NSCLC.[24] Finally, a limitation that still proves hard to overcome is the difficulty to manage the threshold values of the PET/CT parameters. We chose an accepted statistical method to dichotomize the population on the basis of the different PET/CT parameters obtaining statistically significant results with FFR rates. In addition, we run the RMST model to show the influence of continuous PET/CT parameters on FFR time; as shown in Figure 5, the gradients of the curves changed at the threshold values, supporting the reliability of the threshold values calculated, at least in our cohort. Nevertheless, we acknowledge that the threshold values of PET/CT parameters are extremely inhomogeneous in the existing literature; therefore, we deem that it is more appropriate to use these parameters as a continuous variable.

In conclusion, our research supports the hypothesis that the SUV_{mean}, SUV_{max}, and TLG are well correlated with FFR rate in our cohort of pathological stage I adenocarcinoma patients who underwent pulmonary lobectomy (Fig. 6). Therefore, our exploratory study indicates these markers as promising prognostic indicators; further studies are needed to confirm our assessment. We stress the high negative predictive value for recurrence of these PET/CT

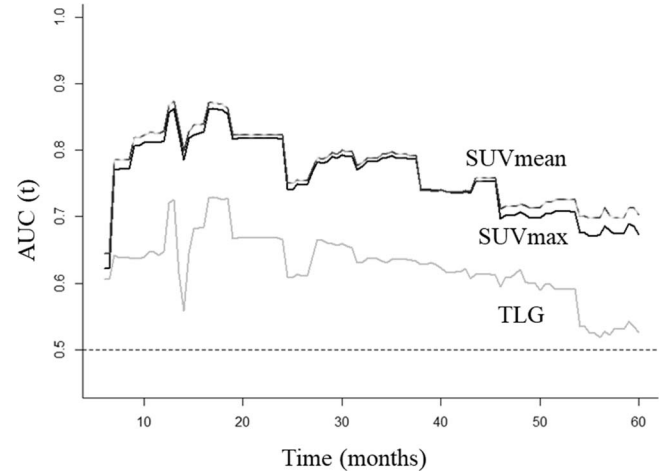

FIGURE 6. Time-dependent AUC curve for prediction of overall survival in patients with early-stage NSCLC according to SUV_{mean} (dashed line), SUV_{max} (black line), and TLG (light grey line).

parameters when a threshold value is selected; this result could help clinicians with planning personalized treatments or dedicated radiological follow-ups.

REFERENCES

1. Wang XY, Zhao YF, Liu Y, et al. Prognostic value of metabolic variables of [^{18}F]FDG PET/CT in surgically resected stage i lung adenocarcinoma. *Medicine (Baltimore)*. 2017;96:e7941.
2. Zhu A, Lee D, Shim H. Metabolic positron emission tomography imaging in cancer detection and therapy response. *Semin Oncol*. 2011;38:55–69.
3. Moon SH, Hyun SH, Choi JY. Prognostic significance of volume-based PET parameters in cancer patients. *Korean J Radiol*. 2013;14:1–12.
4. Adams MC, Turkington TG, Wilson JM, et al. A systematic review of the factors affecting accuracy of SUV measurements. *Am J Roentgenol*. 2010; 195:310–320.
5. Lodge MA. Repeatability of SUV in oncologic (18)F-FDG PET. *J Nucl Med*. 2017;58:523–532.
6. Nakamura H, Saji H, Shinmyo T, et al. Close association of IASLC/ATS/ERS lung adenocarcinoma subtypes with glucose-uptake in positron emission tomography. *Lung Cancer*. 2015;87:28–33.
7. Liu J, Dong M, Sun X, et al. Prognostic value of ^{18}F-FDG PET/CT in surgical non-small cell lung cancer: a meta-analysis. *PLoS One*. 2016;11:e0146195.
8. Dosani M, Yang R, McLay M, 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–e63.
9. Yanarateş A, Yazici B. Los parámetros volumétricos de la PET pueden predecir la supervivencia global en el adenocarcinoma pulmonar avanzado. *Rev Esp Med Nucl Imagen Mol*. 2020;39:3–8.
10. Li Y, Wu X, Huang Y, et al. ^{18}F-FDG PET/CT in lung adenosquamous carcinoma and its correlation with clinicopathological features and prognosis. *Ann Nucl Med*. 2020;34:314–321.
11. Liao S, Penney BC, Wroblewski K, et al. Prognostic value of metabolic tumor burden on ^{18}F-FDG PET in nonsurgical patients with non-small cell lung cancer. *Eur J Nucl Med Mol Imaging*. 2012;39:27–38.
12. Hothorn T, Lausen B. On the exact distribution of maximally selected rank statistics. *Comput Stat Data Anal*. 2003;43:121–137.
13. Lausen B, Hothorn T, Bretz F, et al. Assessment of optimal selected prognostic factors. *Biom J*. 2004;46:364–374.
14. Heagerty PJ, Zheng Y. Survival model predictive accuracy and ROC curves. *Biometrics*. 2005;61:92–105.
15. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics*. 2000;56:337–344.
16. Blanche P, Dartigues J-F, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med*. 2013;32:5381–5397.
17. Rebora P, Salim A, Reilly M. Bshazard: a flexible tool for nonparametric smoothing of the hazard function. *The R Journal*. 2014;6:114–122.
18. Kim DH, Uno H, Wei LJ. Restricted mean survival time as a measure to interpret clinical trial results. *JAMA Cardiol*. 2017;2:1179–1180.
19. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2020. Available at: https://www.R-project.org/. Accessed December 13, 2020.
20. Vansteenkiste J, Fischer BM, Dooms C, et al. Positron-emission tomography in prognostic and therapeutic assessment of lung cancer: systematic review. *Lancet Oncol*. 2004;5:531–540.
21. Cheng G, Huang H. Prognostic value of (18)F-fluorodeoxyglucose PET/computed tomography in non-small-cell lung cancer. *PET Clin*. 2018;13: 59–72.
22. Kirienko M, Cozzi L, Antunovic L, et al. Prediction of disease-free survival by the PET/CT radiomic signature in non-small cell lung cancer patients undergoing surgery. *Eur J Nucl Med Mol Imaging*. 2018;45: 207–217.
23. Ahn HK, Lee H, Kim SG, et al. Pre-treatment ^{18}F-FDG PET-based radiomics predict survival in resected non-small cell lung cancer. *Clin Radiol*. 2019;74: 467–473.
24. Hong IK, Lee JM, Hwang IK, et al. Diagnostic and predictive values of ^{18}F-FDG PET/CT metabolic parameters in *EGFR*-mutated advanced lung adenocarcinoma. *Cancer Manag Res*. 2020;12:6453–6465.