The Role of Histogram-Based Textural Analysis of 18F-FDG PET/CT in Evaluating Tumor Heterogeneity and Predicting the Prognosis of Invasive Lung Adenocarcinoma

Abstract

Objectives: This study aimed to investigate the contributory role of histogram-based textural features (HBTFs) extracted from 18fluor-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) in tumoral heterogeneity (TH) evaluation and invasive lung adenocarcinoma (ILA) prognosis prediction.

Methods: This retrospective study analyzed the data of 72 patients with ILA who underwent 18F-FDG PET/CT followed by surgical resection. The maximum standardized uptake value (SUVmax), metabolic tumor volume, and total lesion glycolysis values were calculated for each tumor. Additionally, HBTFs were extracted from 18F-FDG PET/CT images using the software program. ILA was classified into the following five histopathological subtypes according to the predominant pattern: Lepidic adenocarcinoma (LA), acinar adenocarcinoma, papillary adenocarcinoma, solid adenocarcinoma (SA), and micropapillary adenocarcinoma (MA). Differences between 18F-FDG PET/CT parameters and histopathological subtypes were evaluated using non-parametric tests. The study endpoints include overall survival (OS) and progression-free survival (PFS). The prognostic values of clinicopathological factors and 18F-FDG PET/CT parameters were evaluated using the Cox regression analyses.

Results: The median SUVmax and entropy values were significantly higher in SA-MA, whereas lower in LA. The median energy-uniformity value of the LA was significantly higher than the others. Among all parameters, only skewness and kurtosis were significantly associated with lymph node involvement status. The median values for follow-up time, PFS, and OS were 31.26, 16.07, and 20.87 months, respectively. The univariate Cox regression analysis showed that lymph node involvement was the only significant predictor for PFS. The multivariate Cox regression analysis revealed that higher SUVmax (≥11.69) and advanced stage (IIB-IIIA) were significantly associated with poorer OS [hazard ratio (HR): 3.580, p=0.024 and HR: 7.608, p=0.007, respectively].

Conclusion: HBTFs were tightly associated with clinicopathological factors causing TH. Among the 18F-FDG PET/CT parameters, only skewness and kurtosis were associated with lymph node involvement, whereas SUVmax was the only independent predictor of OS. TH measurement with HBTFs may contribute to conventional metabolic parameters in guiding precision medicine for ILA.

Keywords: Lung adenocarcinoma, prognosis, fluorodeoxyglucose, textural analysis, radiomics
**Introduction**

Lung cancer is the leading cause of cancer deaths worldwide (1). Surgical resection is a radical treatment for early-stage non-small cell lung cancer (NSCLC); however, ~40-60% of patients with early-stage NSCLC die within 5 years following curative resection. Approximately 85% of lung cancer consists of invasive lung adenocarcinoma (ILA), which is the most common histopathological subtype among NSCLC and has a poor prognosis (2). ILA consists of mixed patterns and exhibit highly heterogeneous behavior. The current histopathological classification of ILA fails to meet the advances in imaging, pathology, and tumor molecular biology (3). Additionally, this classification was inefficient for precision medicine development and prognosis prediction. Therefore, in the new classification, ILA is divided into the following five histopathological subtypes based on the dominant pattern: Lepidic adenocarcinoma (LA), acinar adenocarcinoma (AA), papillary adenocarcinoma (PA), solid adenocarcinoma (SA), and micropapillary adenocarcinoma (MA) (3).

Tumor heterogeneity (TH) is one of the important factors that affect treatment response (4). TH, as assessed by 18fluorine-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT), reflects intra-tumoral variances, such as cellularity, proliferation, and necrosis (5). Texture analysis is a set of quantitative parameters that reflect TH using computational processing techniques (6). This analysis shows that heterogeneity is quantitated in all tumor areas in 18F-FDG uptake. With textural analysis, lots of studies have been conducted in various areas, such as benign-malignant distinction (7,8), tumor subtype differentiation (9), treatment response evaluation (10,11), and prognosis prediction (12,13).

Several studies have evaluated the association of histopathological patterns of ILA with conventional 18F-FDG PET/CT parameters, such as maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) (14,15,16). However, studies that investigated the relationship between histopathological patterns of resected ILA and histogram-based textural features (HBFs) extracted from 18F-FDG PET/CT are scarce. Therefore, this study evaluated 18F-FDG PET/CT parameters along with HBFs to evaluate TH and identify independent predictors of progression-free survival (PFS) and overall survival (OS) of ILA. In light of our findings, different postoperative adjuvant treatments for precision medicine can be applied to patients with poor prognostic data.

**Materials and Methods**

**Patients**

The Local Ethics Committee of KTO Karatay University Faculty of Medicine approved this study under the decision number: 2021/010, number: E-41901325-050.99-2306. Patients who underwent an 18F-FDG PET/CT scan before surgical resection with a diagnosis of ILA between August 2012 and September 2019 in our hospital were included in this study. Exclusion criteria were 1) neoadjuvant therapy before surgery, 2) tumor size of <10 mm (to eliminate partial volume effect on PET), (3) tumors with the SUV_{max} lower than the determined MTV threshold of 2.5, 4) mucinous lung adenocarcinoma, and 5) inappropriate condition for 18F-FDG PET/CT (fasting blood glucose of >150 mg/dL). The flowchart of patient selection is shown in Figure 1. Clinicopathological data included age, sex, histopathological subtypes, tumor diameter, lymph node metastasis status, stage, and 18F-FDG PET/CT parameters. The tumor diameter,
nodal involvement, and metastasis (TNM) stage are based on the 8th edition of the American Joint Committee on Cancer TNM classification for lung cancer (17). The following five histopathological subtypes of ILA were determined according to the predominant pattern: LA, AA, PA, SA, and MA. Only two patients had MA patterns, thus they were merged under the SA-MA group, as both solid and micropapillary patterns are considered high-grade.

After the primary tumor resection, all patients underwent regular clinical follow-up, including physical examination and CT or scans every 3-6 months. In cases of abnormal findings on these follow-up examinations, additional imaging studies, including contrast-enhanced CT and 18F-FDG PET/CT scans were performed to verify local, regional, or distant relapse. Therefore, PFS was defined as the time between the dates of pre-operative 18F-FDG PET/CT scan and the date of relapse in patients with relapsed, whereas the time between the date of the 18F-FDG PET/CT scan and the last visit to the hospital for ILA in patients with non-relapsed. The onset for OS was the date of the pre-operative 18F-FDG PET/CT scan. Patient relatives were called by telephone. The telephone follow-up date for the survivors and the date of death for the non-survivors were considered the OS endpoint.

**Imaging**

Patients fasted for 6-8 hours, and 18F-FDG (3.7 MBq/kg) was intravenously injected when their fasting blood glucose was <150 mg/dL. Patients were rested for 60 min after the injection and underwent PET/CT (Biograph LSO-16 PET/CT scanner, Siemens Medical Solutions, Chicago, IL) scan using 18F-FDG. The scan was done from the base of the skull to the upper part of the thigh. CT scan parameters were 120 kV, 140 mAs, and slice thickness of 5 mm. PET acquisition method was 3 min/bed. Images were generated using the reconstruction method with PET and CT. PET/CT fusion images were obtained and transferred to the workstation.

**Image Analysis**

An experienced nuclear medicine physician has visually and semi-quantitatively analyzed 18F-FDG PET/CT images. A region of interest (ROI) was drawn around the tumor to calculate SUV\textsubscript{max} and mean SUV (SUV\textsubscript{mean}) values. A volume of interest with an SUV threshold of 2.5 was used to determine the MTV using the software program (TRUE D, Siemens Medical Solutions). TLG was obtained by multiplying the MTV by the SUV\textsubscript{mean}.

**Textural Analysis**

The 18F-FDG PET images were evaluated by LIFEx v6.30 software, a semi-automatic program for three-dimensional histogram-based textural analysis (18). Figure 2 shows the extraction of tumor HBTFs from 18F-FDG PET images. The SUV\textsubscript{max} threshold of 2.5 was used for tumor segmentation, and the reproducibility of extracted TFs using this value was better compared to other threshold values (19). The TFs obtained from the primary tumor consisted of HBTFs (skewness, kurtosis, energy-uniformity, and entropy). Second- and higher-level TFs were extracted from lesions larger than 64 voxels. However, these parameters were not evaluated as a significant amount of tumors (30/72) in the study population below this level.

**Statistical Analysis**

Study variables were analyzed using Statistical Package for the Social Sciences v26 (IBM Corporation, Armonk, NY, USA). The data were not homogeneously distributed. Therefore, the data were expressed as medians. The Mann-Whitney U test was used for comparisons between paired groups, whereas the Kruskal-Wallis test was for multiple group comparisons. Significance values have been adjusted by the Bonferroni correction for multiple tests.

A Cox regression model including parameters with p values of <0.05 in the univariate analysis was used to
determine covariates for the multivariate analyses. Using these covariates, multivariate Cox regression models were constructed. Hazard ratios (HR) and 95% confidence interval (CI) were calculated. Differences were considered statistically significant at a p value of <0.05.

Results
This study included 72 patients with ILA with a mean age of 63.8±9.7 years, of whom 21 (29.2%) were females and 51 (70.8%) were males. All participants underwent clinically selected appropriate surgical treatment [wedge resection (9), lobectomy (56), and pneumonectomy (7)] in a median duration of 19 (13-32) days after 18F-FDG PET/CT scan. Of these patients, 35 (48.6%) received postoperative adjuvant treatments. The clinicopathological characteristics of patients are summarized in Table 1.

The histopathological subtypes were as follows: 43 (59.7%) AA, 15 (20.8%) SA, 7 (9.8%) LA, 5 (6.9%) PA, and 2 (2.8%) MA. The SUV max, MTV, TLG, energy-uniformity, and entropy values significantly differed between the histopathological subtypes (p values: 0.003, 0.002, 0.003, 0.022, and 0.041, respectively). In post-hoc analyses, the median SUV max and entropy had weak positive correlations with tumor diameter (r=0.742 and 0.709, respectively, both p=<0.001). SUV max and entropy had weak positive correlations with tumor diameter (r=0.305 and p=0.009; r=0.412 and p=<0.001, respectively). Skewness, kurtosis, and energy-uniformity had weak and negative correlation with tumor diameter (r=-0.383, -0.406, and -0.445; p=0.001, <0.001, and 0.003, respectively). Lymph node involvement was observed in 21 (29.2%) patients. Among all parameters, only skewness and kurtosis significantly differed between patients with or without lymph node involvement. In those with lymph node involvement, the median skewness and kurtosis values of the tumor were significantly lower than those without lymph node involvement (median skewness: 2.46 and 1.76, respectively, p=0.009; median kurtosis: 8.78 and 5.29, respectively, p=0.008). Significant differences were found between the stage groups in terms of MTV, TLG, skewness, and kurtosis parameters (p=0.001, 0.001, 0.022, and 0.025, respectively). Higher median MTV and TLG values and lower median skewness and kurtosis values were seen in higher-stage tumors. In post-hoc analyses, differences were observed for MTV and TLG between stages 1A and 2A (p=0.003 and 0.005, respectively).
stages 1A and 2B (both p=0.001), and stages 1A and 3A (both p=0.002). Additionally, differences were observed for skewness and kurtosis between stages 1A and 3A (p=0.038 and 0.021, respectively).

The median values for follow-up time, PFS, and OS were 31.26, 16.07, and 20.87 months, respectively. During the follow-up time, 33 (45.8%) patients had a relapse and 20 (27.8%) patients died. The univariate Cox regression analyses showed that lymph node involvement was the only significant predictor factor for PFS (HR: 2.101, CI: 1.025-4.039, p=0.043) (Table 3). Univariate Cox regression analyses showed that high tumor diameter (≥3 cm), lymph node involvement, high stage (IIB-IIIA), high SUV\text{max} (≥11.69), high MTV (≥9.02 cm$^3$), high TLG (≥48.38 g), low skewness (≤2.18), low kurtosis (≤7.16), low energy-uniformity (≤0.08), and high entropy (≥1.24) were risk factors that affect the OS (Table 4). The multivariate Cox regression analysis revealed that high SUV\text{max} (≥11.69) and advanced stage (IIB-IIIA) was negative independent predictors of OS (Table 5).

**Discussion**

This study investigated the relationship of 18F-FDG PET/CT parameters, including HBTFs, between clinicopathological factors that affect TH and ILA prognosis. Significant differences were found between the conventional parameters of 18F-FDG PET/CT (SUV\text{max}, MTV, and TLG), as well as HBTFs such as entropy and energy-uniformity, and histopathological ILA subtypes. The group consisting of SA and MA had high glycolytic activity and entropy, whereas LA had low glycolytic activity and entropy. Additionally, SA-MA had the lowest energy-uniformity, whereas LA had the highest. Among the 18F-FDG PET/CT parameters, only skewness and kurtosis were associated with lymph node involvement.

TH is an important factor in disease progression and treatment response (20,21). A study that involve patients with advanced lung adenocarcinoma with epidermal growth factor receptor mutation who received tyrosine kinase inhibitor therapy revealed a shorter survival in patients with primary tumors with high entropy values. Additionally, they...
reported that entropy value is an independent predictor of treatment response and decreases after treatment (22). According to Hyun et al. (23) lower entropy was independently associated with longer survival in patients with pancreatic ductal adenocarcinoma. In their study on breast cancer, Aide et al. (13) reported that tumors with high entropy and low energy-uniformity have shorter event-free survival, but the log-rank tests reached almost statistical significance. The evidence is insufficient, but all these results suggest that precision medicine will improve with the use of TFs. Our study revealed entropy and energy-uniformity as predictors of OS, but they were not among the independent predictors for OS and PFS in multivariate Cox regression analysis. Higher SUV_{max} (≥11.69) and advanced stage (IIB-IIIA) was significantly associated with poorer OS in our study population.

### Table 1. Patients characteristics

| Variable               | N   | %   |
|------------------------|-----|-----|
| Age (years)            |     |     |
| <65                    | 35  | 48.6|
| ≥65                    | 37  | 51.4|
| Sex                    |     |     |
| Male                   | 51  | 70.8|
| Female                 | 21  | 29.2|
| Lymph node involvement |     |     |
| Positive               | 21  | 29.2|
| Negative               | 51  | 70.8|
| Stage                  |     |     |
| IA                     | 30  | 41.6|
| IB                     | 3   | 4.2 |
| IIA                    | 4   | 5.6 |
| IIB                    | 15  | 20.8|
| IIIA                   | 20  | 27.8|
| Subtype                |     |     |
| Acinar                 | 43  | 59.7|
| Solid                  | 15  | 20.8|
| Lepidic                | 7   | 9.8 |
| Papillary              | 5   | 6.9 |
| Micropapillary         | 2   | 2.8 |
| Operation type         |     |     |
| Wedge resection        | 9   | 12.5|
| Lobectomy              | 56  | 77.7|
| Pneumonectomy          | 7   | 9.8 |
| Adjuvant therapy       |     |     |
| Yes                    | 35  | 48.6|
| No                     | 37  | 51.4|

### Table 2. Comparison of the median values of {superscript}18F-FDG PET/CT parameters in histopathological subtypes of invasive lung adenocarcinoma groups

| Subtype     | AA     | LA   | PA    | SA-MA  | p value |
|-------------|--------|------|-------|--------|---------|
| SUV_{max}   | 12.07  | 6.82 | 10.68 | 14.89  | 0.003   |
| MTV         | 9.11   | 1.00 | 63.27 | 10.08  | 0.002   |
| TLG         | 48.82  | 4.08 | 275.17| 56.87  | 0.003   |
| Skewness    | 2.10   | 3.22 | 1.91  | 2.14   | 0.094   |
| Kurtosis    | 7.97   | 12.78| 5.06  | 6.14   | 0.081   |
| Energy-uniformity | 0.0714 | 0.1424| 0.0776| 0.0610 | 0.022   |
| Entropy     | 1.1385 | 0.8865| 1.1816| 1.2539 | 0.041   |

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| TLG         | 48.82  | 4.08 | 275.17| 56.87  | 0.003   |
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Table 3. The univariate Cox regression analysis of progression-free survival in patients with invasive lung adenocarcinoma

| Variables     | HRs   | 95% confidence intervals | p value |
|---------------|-------|--------------------------|---------|
| Age (≤65)     | 0.897 | (0.452-1.780)            | 0.757   |
| Sex (male)    | 0.940 | (0.454-1.944)            | 0.867   |
| Lymph node involvement (yes) | 2.101 | (1.025-4.309)            | 0.043   |
| Stage (IIB-IIIA) | 1.920 | (0.957-3.855)            | 0.067   |
| Diameter (≥3 cm) | 1.365 | (0.658-2.832)            | 0.403   |
| SUV_{max} (≥11.69) | 1.246 | (0.625-2.482)            | 0.532   |
| MTV (≥9.02 cm³) | 1.385 | (0.695-2.760)            | 0.354   |
| TLG (≥48.38 g) | 1.104 | (0.556-2.191)            | 0.778   |
| Skewness (≥2.18) | 1.267 | (0.636-2.525)            | 0.501   |
| Kurtosis (≥7.16) | 1.229 | (0.869-1.738)            | 0.243   |
| Energy-uniformity (≥0.08) | 1.486 | (0.743-2.972)            | 0.262   |
| Entropy (≥1.14) | 1.763 | (0.880-3.532)            | 0.110   |

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Table 2. Comparison of the median values of {superscript}18F-FDG PET/CT parameters in histopathological subtypes of invasive lung adenocarcinoma groups

Entropy and energy-uniformity quantitatively characterize the TH from various perspectives. Entropy refers to the randomness of voxel intensity distribution within the ROI. Entropy increases as the intensities of pixels are chaotically distributed. Energy-uniformity measures the number of repeated pairs. Thus, it reflects the distribution uniformity. This parameter is expected to increase as the number of repeated pixel pairs increases (21). Our findings suggest that SA-MA subtypes have high TH and higher metabolism, whereas LA is more homogeneous with a lower metabolism. Previous study that examine the relationship between the
Histopathological subtypes of ILA and SUV<sub>max</sub> report that SA had higher SUV<sub>max</sub> than LA (24). The presence of the SA or MA subtype is a poor prognostic factor (25). According to these findings, the poor prognosis of the SA-MA group may be due to TH and higher metabolic activity.

Among all 18F-FDG PET/CT parameters, only skewness and kurtosis were significantly different in lymph node involvement. These parameters show the distortion or disparity of the histogram that is relative to the normal distribution (18). A recent study described a machine learning-based TFs model as a reliable method for predicting axillary lymph node metastasis in invasive ductal breast cancer (26). Li et al. (27) found that skewness was the most ideal predictor for pelvic lymph node involvement in cervical squamous cell carcinoma. Our previous study revealed that a high-order TF showing the distribution of short homogeneous regions with low gray levels had an independent association with axillary lymph node metastasis unlike other parameters of 18F-FDG PET/CT in invasive ductal breast cancer (28).

However, texture analysis still has a reproducibility barrier to overcome before its clinical practice implementation (14,29). Additionally, TFs that are the most reliable indicator of TH for different tumor types are unclear. HBTFs are based on the analysis of the SUV histogram within the entire tumor. These parameters may have higher chances of clinical applicability in the future because of their simplicity and accessibility compared to more complex higher-order TFs. Most of the TFs are affected by tumor segmentation methods. The present study used the threshold of SUV of 2.5 for the tumor segmentation since the reproducibility of extracted TFs using this threshold was better than that of other thresholds (19). Various tumor segmentation techniques, such as manual or threshold-based methods, are used in the studies; however, no consensus is available on the most appropriate method for 18F-FDG PET/CT textural analysis.

### Study Limitations

Limitations of the study include the retrospective design, small sample size, and single-institution experience. Additionally, we cannot extrapolate the findings to patients with advanced stage ILA.

### Conclusion

High stage and high SUV<sub>max</sub> were independent risk factors for OS in patients with ILA. The homogeneity of LA and the heterogeneity of SA-MA were quantified by HBTFs. Lymph node involvement was predicted by skewness and kurtosis. Therefore, HBTFs may improve the prognostic value of 18F-FDG PET/CT by contributing to the quantification of TH. If confirmed by larger, prospective, and multi-center studies, extracted HBTFs from 18F-FDG PET/CT could potentially become non-invasive prognostic imaging biomarkers to guide precision medicine.

### Ethics

**Committee Approval:** The Local Ethics Committee of KTO Karatay University Faculty of Medicine approved this study under the decision number: 2021/010, number: E-41901325-050.99-2306.

**Informed Consent:** The informed consent form was obtained from the patients or their relatives who participated in the study.

**Peer-review:** Externally peer-reviewed.
Authorship Contributions
Surgical and Medical Practices: H.Ö., M.İ.E.K., Concept: H.Ö., M.İ.E.K., N.C., Design: H.Ö., N.C., Data Collection or Processing: H.Ö., N.C., Analysis or Interpretation: H.Ö., N.C., Literature Search: H.Ö., N.C., M.E., M.İ.E.K., Writing: H.Ö., N.C., M.E., M.İ.E.K.

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