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The comparison of SUV_{max} values in ^{18}F-FDG PET/CT according to cell type, stage, lymph node involvement and metastasis in lung cancers

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ABSTRACT

Aims: ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography/computerized tomography (PET/CT) provides metabolic information in addition to anatomic extension. This study aimed to compare the primary tumor maximum standardized uptake values (SUV_{max}) on PET/CT according to the histopathological type, stage, nodal involvement, and the metastasis of lung cancers.

Methods: In this retrospective study, PET/CTs of the patients with lung cancer were examined. Staging of the cancer was performed according to the eighth (8th) edition of the tumor, node and metastasis (TNM) classification system. SUV_{max} values were recorded and compared.

Results: Two hundred thirty-three patients with lung cancer (78.5% male, mean age: 67.0±9.6 years, range: 47-91 years) were analyzed. The SUV_{max} value of squamous cell carcinoma (SCC) (15.2±7.6) was higher than the SUV_{max} values of adenocarcinoma (AC) and small cell lung carcinoma (SCLC) (10.9±5.6 and 12.2±5.5, respectively, p<0.001). SUV_{max} values were not different between the stages of AC, SCC and SCLC (p=0.285, p=0.377 and p=0.061, respectively). SUV_{max} values were similar between nodal involvements (p=0.490, p=0.645 and p=0.114 for AC, SCC, and SCLC, respectively). There was no difference in SUV_{max} values of lung cancers with and without metastasis (p=0.496, p=0.209, and p=0.544 for AC, SCC, and SCLC, respectively).

Conclusions: The SUV_{max} value of SCC was highest among lung cancers. There was no significant difference between the SUV_{max} value of the primary tumor on PET/CT and the TNM stages of the tumor.

Introduction

Lung cancer ranks first both in the incidence of cancer and in cancer-related deaths in men (1). It is the second most commonly diagnosed cancer and the third most common cause of cancer-related deaths in women (1). 5-year survival has been reported as 5.2% in metastatic disease and 57.4% in localized disease (2). Staging in lung cancer is very important as it determines the prognosis. Despite the improvements in diagnosis, most lung cancers have advanced stage disease when diagnosed. Approximately, less than one third of patients with non-small cell lung cancer (NSCLC) are treated with surgery (3). Currently, eighth (8th) tumor, node and metastasis (TNM) staging system is used for lung cancer (4).

Warburg evaluated the shift in energy production from oxidative phosphorylation to glycolysis as an essential feature of the cancer cell in 1930 (5). Positron emission tomography (PET) using ^{18}F-fluoro-2-deoxy-D-glucose (FDG), a functional imaging technique utilizing this glycolytic change, is widely used and recommended as an aid in cancer diagnosis and staging (5,6). FDG PET/computed tomography (CT) provides functional and metabolic information about lung cancer and the European Society of Thoracic Surgeons guideline has reported that its

sensitivity and specificity in lymph node staging are 80-90% and 85-95%, respectively, and its negative predictive value is quite high in peripheral NSCLC (7).

Small cell lung cancer (SCLC) was classified as local and advanced disease in the past. The International Association for the Study of Lung Cancer recommended the use of the TNM staging for SCLC and NSCLC in 2007 (8). TNM classification was chosen for SCLC in this study.

Standardized uptake value (SUV) is a simple computable parameter indicating quantitative FDG uptake in tissue and tumor (9). FDG uptake in the tumor is calculated with the maximum SUV (SUV_{max}), which gives information about the activity of the disease or the aggressiveness of the tumor (10). Many factors such as blood glucose level, body weight, lesion size, respiratory movement and histological type of the lesion affect the SUV_{max} value. The SUV_{max} value varies greatly even in the same tumor type and this problem is especially detected in lung cancers and causes difficulties in diagnosis and staging (11,12). In the case of active infection, inflammation, previous lymph node sampling, sarcoidosis, anthracosis, and reactive lymph nodes, there may be false positivity in PET/CT. False negativity may occur in carcinoid tumors and adenocarcinomas (AC).

This study aimed to compare SUV_{max} values in lung cancers according to cell type, staging, lymph node involvement and metastasis. The SUV_{max} values of the cell types were also compared according to the disease stage, lymph node involvement and metastasis.

Methods

This retrospective cohort study was conducted by the Clinical Research Ethics Committee of the Umraniye Training and Research Hospital (approval no: 37, date: 20.03.2019). The study included the patients who were newly diagnosed with lung cancer. The lung cancer diagnosis was obtained with pathological examination of tissue biopsies. The diagnostic approach was decided according to the location of the lesion in the lung or the mediastinal lymph node involvement on CT or PET/CT. CT-guided needle biopsy was performed in peripheral lesions and flexible bronchoscopy was preferred in central lesions first. Convex endobronchial ultrasonography (EBUS) was performed for both diagnosis and staging in patients with mediastinal lymph nodes detected on CT or PET/CT. When EBUS was not diagnostic, patients underwent mediastinoscopy. Patients with early-stage lung cancer underwent surgery and they were diagnosed with excisional biopsy. US-guided biopsy was performed for supraclavicular lymph node or liver metastasis. 760 patients with ICD code-34, who underwent ^{18}F-FDG PET/CT between October 2016 and December 2018, were analyzed retrospectively. Five hundred twenty seven patients who underwent PET/CT for the evaluation of response to treatment, who had benign lesions in the pathology reports, who discontinued follow-up, and whose pathology reports could not be reached were excluded from the study. Two hundred thirty-three patients with lung cancer were included in the study. PET/CTs of the patients with pathologically diagnosed lung cancer were examined retrospectively and lung cancers were staged according to the 8th TNM system (13). SUV_{max} values were recorded. Lymph node involvement was classified as N0, N1, N2 and N2 (14). Metastasis (M1a: regional, M1b: solitary extrathoracic, M1c: multiple extrathoracic) was classified as present or absent.

PET/CT Procedure

FDG infusion (nearly 370 MBq of ^{18}F FDG) was applied after the patients fasted for at least six hours and the measurement of normal peripheral blood glucose or below 200 mg/dL. Approximately 60 minutes after the injection (15), ^{18}F-FDG PET/CT was performed using an integrated PET/CT scanner (Discovery ST, GE Medical Systems). Non-contrast enhanced whole body CT scans were performed using a 16-sliced helical CT scanner before the acquisition of the PET image. Images were obtained from head to mid-thigh with 6-9 bed positions (2 minutes for each bed position). The images were reconstructed in different imaging views, that is, in cross-sectional, axial, sagittal, and coronal planes. All SUV measurements were normalized for patient body weight. SUV_{max} >2.5 was considered positive. All scans were interpreted by two experienced nuclear medicine physicians.

Statistical Analysis

The patient data collected in the study were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS, Chicago, IL, USA) package program. Frequency and percentage for discrete data and mean±standard deviation for continuous data were used as descriptive values. The “independent sample t-test” was used for comparison of two groups and “ANOVA test” was used to compare three or more groups. Results were considered statistically significant when the p value was less than 0.05.

Results

The study included 233 patients with pathologically diagnosed lung cancer. Diagnoses of 115 patients were AC, 81 had squamous cell carcinoma (SCC) and 37 had SCLC (Table 1). The patients’ mean age was 67.0±9.6 years and 183 of them (78.5%) were male.

The SUV_{max} value of SCC (15.2±7.6) was higher than the SUV_{max} values of AC and SCLC (10.9±5.6 and 12.2±5.5, respectively, $p<0.001$, Table 2). Post-hoc tests suggested that it was associated with the differences between the SUV_{max} values of AC and SCC and between the SUV_{max} values of SCLC and SCC.

SUV_{max} values were not different between the stages (1, 2, 3A, 3B, 3C and 4) of AC, SCC and SCLC (p=0.285, p=0.377 and p=0.061, respectively, Table 3). There were significant differences in SUV_{max} values of histopathological types in stage 1, stage 3A and stage 4, (p=0.016, p=0.008 and p=0.001, respectively) and the SUV_{max} values of SCLC in stage 1, SCC in stage 3A and stage 4 (28.1±0.1, 14.4±6.1 and 16.9±7.9, respectively) were highest. Post-hoc test showed that the SUV_{max} values of SCLC and SCC and the SUV_{max} values of SCLC and AC types in stage 1, the SUV_{max} values of AC and SCC in stage 3A and the SUV_{max} values of SCC and AC in stage 4 were statistically different.

SUV_{max} values were similar between nodal involvements (N0, N1, N2 and N3) (p=0.490, p=0.645 and p=0.114 for AC, SCC, and SCLC, respectively, Table 4). Significant differences for SUV_{max} values were observed in N1, N2 and N3 between the cell types (p=0.007, p=0.047 and p=0.004, respectively). Post-hoc test determined that the differences were caused by AC and SCC for N1, SCLC and SCC for N2, and SCC and AC for N3.

There was no difference in SUV_{max} values of lung cancers with and without metastasis (p=0.496, p=0.209 and p=0.544 for AC, SCC and SCLC, respectively) (Table 5). SUV_{max} of SCC (16.9±7.9) was the highest among metastatic cancers (p=0.001) and SUV_{max} of AC (10.5±6.1) was the lowest among non-metastatic cancers (p=0.007). Post-hoc test determined that the difference was caused by SCC and AC in patients with and without metastasis.

Table 1. Demographic data of the patients and histopathological cell types of lung cancers

Age, years, (mean±SD)	67.0±9.6
Gender, male, n (%)	183 (78.5)
Histopathological cell type, n (%)	
Adenocarcinoma	115 (49.4)
Squamous cell carcinoma	81 (34.8)
Small cell lung carcinoma	37 (15.9)
Total	233 (100)

SD: Standard deviation, n: Number

Table 2. The comparison of SUV_{max} values according to the histopathological cell type

Cell type	SUV_{max}, (mean±SD)*
Adenocarcinoma	10.9±5.6
Squamous cell carcinoma	15.2±7.6
Small cell lung carcinoma	12.2±5.5

*p<0.001 for within group differences. SUV_{max}: Maximum standardized uptake value, SD: Standard deviation

Discussion

Lung cancer is a heterogeneous disease with highly variable prognosis and course. Staging plays an important role in guiding prognosis and treatment. TNM staging is currently the only classification method used in lung cancer. However, the different prognosis of even patients at the same stage cannot be explained by TNM staging determined according to anatomical features. PET/CT may provide additional benefit in the prediction of prognosis since it also indicates metabolic properties of the tumors (8,16). Because the TNM staging also determines the treatment of the disease in addition to prognosis, PET/CT may be included in the current staging system. The SUV_{max} value, which shows the metabolic activity of the primary tumor, has been shown to have a prognostic significance in NSCLC (17). In our study, a correlation was found between histopathologic cell types of lung cancer and SUV_{max} values. The SUV_{max} value of SCC type was significantly higher than the other lung cancer types. Similar to our study, SUV_{max} mean values were previously reported in the range of 2.5-19.1 and 0.4-28.4 in SCC and AC cell types, respectively, and the difference was statistically significant (18). In a retrospective evaluation of 176 NSCLC patients, the SUV_{max} value of SCC was statistically significantly higher than that of AC (14.8 vs. 8.6, respectively) (19).

Sahiner et al. (16) showed a positive correlation between SUV_{max} values and stages of lung cancer, without separating them according to cell types in a retrospective study including 168 patients. Due to the partial volume effect, they have stated that SUV_{max} can be detected lower than expected in small lesions, and when those with lesion size <2.5 mm was excluded from the evaluation, they reported that there was no correlation between SUVmax and stages (16). When the stages of lung cancer cell types were compared according to SUV_{max} values, no difference was found between SUV_{max} values in the present study. There was no difference in SUV_{max} values between early and advanced stage tumors in all lung cancer histopathologic cell types. In addition, comparisons were made between SUV_{max}

Table 3. The comparison of SUV_{max} values according to the TNM stage of the lung cancers

Stage	**Stage 1** (n=21)	**Stage 2** (n=31)	**Stage 3A** (n=32)	**Stage 3B** (n=27)	**Stage 3C** (n=17)	**Stage 4** (n=105)	**p**
Adenocarcinoma	8.5±3.8 (n=9)	11.6±4.9 (n=14)	8.0±3.5 (n=11)	12.4±10.9 (n=8)	12.8±5.6 (n=6)	11.2±5.3 (n=67)	0.285
Squamous cell carcinoma	12.6±3.8 (n=11)	14.3±7.5 (n=15)	14.4±6.1 (n=16)	14.6±6.1 (n=11)	21.3±15.2 (n=4)	16.9±7.9 (n=24)	0.377
Small cell lung carcinoma	28.1±0.1 (n=1)	12.8±4.3 (n=2)	10.1±2.1 (n=5)	11.1±5.2 (n=8)	11.2±3.1 (n=7)	12.9±6.2 (n=14)	0.061

SUV_{max}: Maximum standardized uptake value, n: Number

Table 4. The comparison of the SUV_{max} values according to the lymph node involvement

Lymph node involvement	N0 (n=66)	N1 (n=19)	N2 (n=53)	N3 (n=95)	p
Adenocarcinoma	11.2±5.4 (n=34)	9.6±3.9 (n=12)	12.1±8.1 (n=25)	10.3±4.3 (n=44)	0.490
Squamous cell carcinoma	13.9±7.4 (n=29)	15.5±4.0 (n=7)	16.8±7.6 (n=19)	15.5±8.7 (n=26)	0.645
Small cell lung carcinoma	17.9±9.4 (n=3)	- (n=0)	10.3±2.5 (n=9)	12.3±5.5 (n=25)	0.114

SUV_{max}: Maximum standardized uptake value, n: Number

Table 5. The comparison of SUV_{max} values according to the metastasis

Metastatic disease	No metastasis (n=128)	Metastasis (n=105)	p
Adenocarcinoma	10.5±6.1 (n=48)	11.2±5.3 (n=67)	0.496
Squamous cell carcinoma	14.5±7.5 (n=57)	16.9±7.9 (n=24)	0.209
Small cell lung carcinoma	11.8±5.1 (n=23)	12.9±6.2 (n=14)	0.544

SUV_{max}: Maximum standardized uptake value, n: Number

values of different cell types within each stage and there was a significant difference in stage 1, 3A and 4.

The size increase in the primary tumor, SUV_{max}>9, central localization and vascular invasion were reported to be associated with lymph node involvement in the study evaluating 159 patients and 1001 lymph node stations, by Billé et al. (20). In addition, when lymph node size was ≥1 cm, the sensitivity of PET/CT was 85% in the evaluation of malignant invasion (20). Although PET/CT is more useful than other imaging techniques in lymph node metastatic evaluation, it has been reported that PET findings cannot substitute for histological examination because there may be false negative and positive results (21). In a study conducted with 80 patients with NSCLC, the SUV_{max} value of the primary tumor was significantly related to lymph node involvement (22). In N0, N1, and N2 lymph node involvements, the primary tumor SUV_{max} values were 5.8±4.8, 8.1±5.1, and 8.7±3.4, respectively (p=0.036) (22). Similarly, a positive correlation was shown between the primary tumor SUVmax value and lymph node metastasis in another study (18). When the SUV_{max} value of primary tumor was ≥12, lymph node metastasis was detected in 70% of the patients; however, the frequencies of lymph node metastasis of SCC and AC tumor types were not different (18). In present study, there was no difference in SUV_{max} values between lung cancer cell types according to lymph node involvement. However, there was a statistically significant difference in the SUV_{max} values of lymph node involvement for N1, N2 and N3 according to tumor types. Especially for N1 and N3 lymph node involvement, it was determined that the SUV_{max} value of SCC was significantly higher than that of AC.

Each unit increase in the SUV_{max} value of the primary tumor was reported to increase the probability of metastasis approximately 1.5 times (23). Cerfolio et al. (24) reported that SUV_{max} was an independent marker for predicting recurrence, survival, and distant organ metastasis. When lung cancer histopathological cell types were evaluated according to metastasis status, SUV_{max} values were not different in our study; on the other hand, when metastasis was evaluated according to cell types, a positive correlation was revealed, and this was caused by the SCC cell type.

The limitations of this study were that it was a single-center, retrospective study, and parameters such as metabolic tumor volume and total lesion glycolysis, which have been reported to have prognostic significance in PET/CT except for SUV_{max} (25) were not available. Another limitation was the small sample size, limiting the generalizability of the findings to other populations.

Conclusion

This study showed that SUV_{max} value of SCC was highest among lung cancers. SUV_{max} values of the histopathological types of lung cancer were similar in terms of the stages, lymph node involvement and presence of metastasis. No relationship between the SUV_{max} value of the primary tumor on PET/CT and the TNM stages of the tumor was recorded.

Ethics

Ethics Committee Approval: We obtained permission from the Clinical Research Ethics Committee of the Umraniye Training and Research Hospital (approval no: 37, date: 20.03.2019).

Informed consent: Informed consent was waived because of the retrospective design of the study.

Peer-review: Externally peer-reviewed

Authorship Contributions

Concept: T.Ç., K.C., E.G.I., Design: T.Ç., K.C., E.G.I., Data Collection or Processing: T.Ç., K.C., Analysis or Interpretation: T.Ç., K.C., Literature Search: K.C., E.G.I., Writing: T.Ç., K.C.

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