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# Diagnostic and clinical value of F-18 FDG PET/CT in thoracic carcinoid tumors

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## ABSTRACT

**Aim**: To assess the correlation between standard uptake values (SUVmax, SUVmean) and Ki-67 in typical lung carcinoid (TC) tumors.

**Methods**: Thirty-eight patients with thoracic masses sent for diagnosis and staging were included in the study. F-18 FDG PET / CT was applied to all patients before the operation. The patients were operated by thoracic surgery clinic. By determining different cut-off values (2.5 and 0.5), SUVmean and SUVmax values of the lesions from the curves drawn to the area of interest were calculated.

**Results**: Thirty-eight patients were included in the study (18 women, 20 men). The average age of our patients was 45. Pathological diagnoses of all patients were determined as typical carcinoids. Eight of our patients had parenchymal lesions and twenty of them had endobronchial lesions. The average of the Ki-67 index was about 3-4% (range 1-10%). No recurrence or death was detected after resection in the 5-year follow-up period. SUVmean1 and SUVmean2 values were statistically significant when compared with SUVmax1 and SUVmax2 values ($p < 0.05$).

**Conclusion**: We think that the SUVmean and Ki-67 index may be an important prognostic indicator that identifies high-risk subgroups. It is thought that Ki-67 indices may correlate well with SUVmean values, and low cut-off values may be more suitable for diagnosis and prognosis in typical carcinoid tumors. SUVmean values can be used for lung carcinoid tumors and F-18 FDG PET/CT imaging is useful in the approach to carcinoid tumors of the lung before thoracic surgery.

**Key words:** Lung cancer, carcinoid tumors, F-18 FDG PET / CT, SUVmean, Ki-67.

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## Introduction

Lung cancer is the most common type of cancer and one of the leading causes of cancer death. Apart from lung cancer subtypes, carcinoid tumors from neuroendocrine tumors (NET) located in the thorax are relatively slow-growing tumors with fine contours and good prognosis [1]. Lung carcinoid tumors constitute 20% of lung carcinomas and their incidence has increased in recent decades with the development of imaging methods that provide early diagnosis. They are malignant tumors originating from mature cells of the pulmonary diffuse neuroendocrine system, showing neuroendocrine morphology and differentiation. These tumors, which have distinctive clinicopathological features, are classified as low grade typical carcinoid tumors and intermediate grade ones as atypical carcinoid (AC) tumors [1]. Carcinoid

tumors are rare tumors that constitute 1-2% of all lung cancers and 20-25% of all body carcinoids. Although its estimated age-adjusted incidence is between 0.2 and 2 per 100,000, its prevalence in men and women has increased by approximately 6% per year over the past 30 years [2]. It is said that this increase may be related to the development of diagnostic methods and the widespread use of immunohistochemistry. Lung NETs are staged according to the AJCC/IASLC TNM staging system. In addition to conventional imaging and scintigraphy, positron emission tomography (PET), multiphase computed tomography (CT) and magnetic resonance imaging (MRI) should be used for accurate staging [2, 3].

18 F-fluorodeoxyglucose positron emission tomography (FDG-PET) is the used for diagnosis of carcinoid tumors [4]. In the differential diagnosis of carcinoid tumors, the prevalence of which has increased in recent years, from lung masses, it is aimed to reflect the additional information and metabolic data to be provided by F-18 FDG PET/CT to the clinic, to identify some determinative features in the diagnosis of carcinoid tumors, and to include them in clinical practice to contribute positively to the prognosis of the patients [4, 5]. In their study published in the 2023 edition of the Annals of Nuclear Medicine by Flavia Linguanti et al., the prognostic significance of volumetric and semiquantitative parameters measured using [18F]FDG PET/CT imaging in patients with typical lung carcinoids and their relationship with the proliferative index (Ki-67) were evaluated [6]. Semi-quantitative and volumetric parameters assessed utilizing [18F]FDG PET/CT and SSTR imaging combined with Ki-67 can provide a reference for prognostic assessment of patients with TC to better stratify risk groups for developing individualized therapeutic strategies [7-9].

Ki-67 proliferation index is a proliferation marker expressed in neoplastic cells. The percentage of cells expressing Ki-67 is expressed as a proliferation index [10]. In the WHO publication in 2021, the Ki-67 proliferation index was not included in the diagnostic criteria in the grade classification of NETs [11]. There are studies showing that the Ki-67 proliferation index and SUV values have a prognostic value in some cancers. Recent studies have reported that it may be beneficial to specify the Ki-67 proliferation index in preoperative biopsies, since the width of surgical resection may vary depending on the histopathological subtype [10-12].

Low F-18 FDG uptake is expected in typical carcinoid tumors. In current study, we goaled to show the compatibility of SUVmax and SUVmean values of integrated FDG-PET/CT calculated with different cut-offs in typical carcinoid tumors with clinical and pathological findings.

## Materials and methods

The study was initiated after the approval of Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee (Approval date and No: 31/08/2023 / 20.478.486/ 1965). Our research is a retrospective study. Between February 2012 and January 2023, 38 patients who had F-18 FDG PET&CT examinations, had an intrathoracic mass and were diagnosed with typical carcinoid tumor by surgical resection were included in the study.

F-18 FDG PET/CT was applied to all patients for diagnosis and staging before surgery. Patients were fasted for at least 6 hours before 18F-FDG injection. The blood glucose levels of all patients were checked before the injection, and if the blood glucose level was below 200 mg/dL, 0.1-0.2 mCi/kg 18F-FDG injections were made. After lying in the supine position under the

camera, 18F-FDG PET/CT imaging was performed on GE Healthcare IQ Discovery PET/CT devices approximately 1 hour after the injection. After low-dose CT (140 kV and 50 mAs), PET image (6-8 beds, 2 min/bed) was taken from the vertex to the upper thigh. Images were taken from the patients at the 2nd hour of the injection.

Lymph node metastases and distant metastases were not detected. Ki-67 proliferation index was calculated. Standard uptake values (SUVmax, SUVmean) were compared before and after surgery in TC tumors. By determining different cut-off values (2.5 and 0.5), SUVmax and SUVmean values of the lesions were calculated from the curves drawn to the area of interest. We make the routine reporting according to the 2.5 cut-off SUVmax and interpret it in favor of malignancy. Drawings were made by taking only the lesion area of interest, excluding atelectatic areas. Calculations were made using the tumor tracking program.

***Statistical analysis:*** Statistical analyzes were performed using the SPSS 22.0 (Statistical Package for the Social Sciences) program. Descriptive statistics were presented as mean ± standard deviation for those with normal distribution, as the median value in the min-max range for those who were not normally distributed, and as n numbers and percentages for those with nominal distribution. Pearson chi-square / Fisher Exact Test were used in the analysis of nominal variables. ROC Analysis was performed to determine the diagnostic competence of numerical variables. For $p<0.05$, the results were considered statistically significant.

## Results

Of the 38 patients included in the study, 18 were female (47.4%) and 20 were male (52.6%). The mean age was 45±2.4 years.

Pathological diagnosis of all patients was found to be typical carcinoid. Thirteen of our


**Figure 1.** SUVmean and SUVmax values of the patients.

patients had parenchymal lesions and twenty-five had endobronchial lesions.

The mean of the Ki-67 index was approximately 3-4% (range 1-10%). When ROC analysis was performed for Ki-67 proliferation index, the best cut-off value in terms of survival was found to be 4%.

PET/CT scan results were interpreted as positive when lesion activity was greater than background mediastinal and lung activity. No recurrence or death was detected after resection during the follow-up period. SUVmean and SUVmax values are shown in figure 1.

SUVmean1 and SUVmean2 values were statistically significant when compared with SUVmax1 and SUVmax2 values ($p < 0.05$) (Table 1).

common in female patients. Contrary to the literature, in our study, 53.6% of the patients were male and 46.4% were female. Although bronchopulmonary carcinoid tumors can occur at any age, patients are usually between the ages of 45-55 at the time of diagnosis [16]. The mean age of occurrence of typical carcinoid tumors is 45, while that of atypical carcinoid tumors is 55 [10]. In our study, the mean age of patients with typical carcinoid tumors was 45±2.4 years.

Bronchopulmonary carcinoid tumors exhibit low activity on F-18 FDG PET/CT, showing less F-18 FDG uptake than expected for malignant tumors. F-18 FDG uptake of TC and AC tumors varies according to the number of mitoses and tumor proliferation. In recent studies, it was concluded that the tumor SUVmax threshold

**Table 1.** Comparison of the SUVmax and SUV mean levels in different cut-off values.

| **Parameters** | **Cut-off value: 2.5** | **Cut-off value: 0.5** | ***P* value** |
|---|---|---|---|
| **SUVmax** | 5,35±2,72 | 5,35±2,72 | >0.05 |
| **SUVmax (min-max)** | 2,64 -11,06 | 2,64 -11,06 | >0.05 |
| **SUVmean** | 3,36±0,76 | 2,02±0,89 | **<0.05** |
| **SUVmean (min-max)** | 2,62 – 4,58 | 1,17 – 4,15 | **<0.05** |

## Discussion

Neuroendocrine neoplasms of the lung are classified as low grade (Typical carcinoid), middle grade (Atypical carcinoid) and high grade tumors according to clinicopathological behavioral characteristics [13]. Atypical carcinoid tumors are the rarest of the neuroendocrine neoplasms of the lung. Typical carcinoid tumors are approximately 8-10 times more common than atypical tumors [13, 14]. 100% of the patients in our study had a typical carcinoid tumor.

Bronchopulmonary carcinoid tumors occur equally in both sexes [15]. There are also studies indicating that typical carcinoid tumors are more

values of 1.5 and 2.5 detected the tumor at a high rate [17, 18]. In our study, we calculated the SUVmax and SUVmean values of the lesions from the curves drawn on the area of interest by determining different cut-off values (2.5 and 0.5). We made the routine reporting according to the 2.5 cut-off SUVmax and interpreted in favor of malignancy.

In their study investigating the diagnostic and prognostic effect of F-18 FDG PET/CT in pulmonary neuroendocrine tumors, Chong et al. found that the SUVmax value of bronchopulmonary carcinoid tumors ranged between 1.7-7.1 (mean SUVmax value=4). They found that survival was reduced in cases where the SUVmax value of high-grade

bronchopulmonary carcinoid tumors was above 13.7 [19]. There is no study in the literature for an SUVmax threshold value with prognostic value for survival for bronchopulmonary carcinoid tumors. In our study, the SUVmax value was 5.35±2.72, and we think that this value is positive in terms of survival, since all patients survived.

Ki-67 is a nuclear antigen expressed on proliferating cells and can be clearly detected in bronchopulmonary carcinoid tumors [20, 21]. A high Ki-67 proliferation index has been described as a poor prognostic factor for survival [20, 21]. There are suggestions that the Ki-67 proliferation index should be used as a prognostic factor in bronchopulmonary carcinoid tumors and should also be the criterion of the grade classification system. However, its precise role and use have not yet been defined and included in the WHO classification criteria [22]. In addition to studies showing that the Ki-67 proliferation index is not associated with survival, there are also studies showing its prognostic value and its relationship with metastasis and recurrences [22, 23]. There are studies showing that the Ki-67 index is successful in predicting prognosis with threshold values ranging from 2.5% to 5.8%. The most used values are the 4% and 5% threshold values because they are more reliable [24, 25]. Filosso et al., in their study examining prognostic factors and survival outcomes in bronchopulmonary carcinoid tumors, found that Atypical Carcinoids had a statistically significantly higher Ki-67 proliferation index than typical carcinoids [20]. They found that tumors with a Ki-67 index over 6% had a higher risk of lymph node metastasis and recurrence. They stated that they were of the opinion that prospective studies should be conducted for adjuvant treatment in patients with a high Ki-67 index [20]. Marchevsky et al. found the best Ki-67 cut-off value as 5% in terms of overall survival, recurrence-free survival, recurrence time and recurrence rates in TC tumors. When they grouped typical carcinoids according to this threshold value, they found that the overall and recurrence-free survival was worse and the time to recurrence was shorter in the group with a Ki-67 proliferation index above 5%. They suggested that a new classification integrating the Ki-67 proliferation index and the WHO classification could be useful in determining prognosis and treatment [23]. Grimaldi et al., in their study in which they examined bronchopulmonary carcinoid tumors according to Ki-67 proliferation index, performed ROC analysis to determine the best Ki-67 value in terms of recurrence risk. They found the optimal Ki-67 cutoff value as 4% with a sensitivity of 79% and a specificity of 83% [24].

Marchio et al., in their study investigating the role of Ki-67 proliferation index in bronchopulmonary carcinoid tumors, found that the 4% threshold value for the Ki-67 index had prognostic power in terms of overall and recurrence-free survival [26]. In our study, the mean value of Ki-67 proliferation index was approximately 3-4% (range 1-10%), similar to the literature. When ROC analysis was performed for Ki-67 proliferation index, the best cut-off value for typical carcinoid tumor was found to be 4% in terms of survival. In cases where the Ki-67 index is found above 4% in preoperative biopsy or intraoperative frozen section, the width of surgical resection and the need for adjuvant treatment can be decided considering the higher risk of recurrence. In addition, these tumors may require closer and longer follow-up.

Our study has some limitations. The limitations of the study are that it is retrospective and the sample size is small. However, our study is valuable in terms of the fact that little work has

been done on this subject in Turkey and it supports future studies.

## Conclusions

F-18 FDG PET/CT imaging has an important role in the diagnosis and staging of typical parenchymal and bronchial carcinoids. We think that SUVmean and Ki-67 index may be an important prognostic indicator that defines high-risk subgroups in lung typical carcinoid tumors. We think that Ki-67 indices can be well correlated with SUVmean values, and the use of low cut-off values in typical carcinoid tumors may be more appropriate for diagnosis and prognosis. It has been predicted that SUVmean values calculated with a low cut-off value in typical carcinoid tumors of the lung may yield more consistent results in terms of clinical and pathological diagnosis.

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