

Diagnostic value of ^{18}F -FDG-PET/CT in benign lung diseases

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Abstract

Introduction: There are many diseases which, despite not being malignant, show high metabolic activity and cause false-positive results.

Aim: To evaluate the results of positron emission tomography (PET) in patients who underwent resection after preliminary diagnosis of malignancy based on fluorodeoxyglucose (FDG) uptake value, in whom the lesions were later classified as pathologically benign.

Material and methods: The analysis included the records of 106 (12.3%) patients out of 862 patients who underwent surgery between January 2012 and December 2015 after being initially diagnosed with malignant lung lesions based on PET-CT results, in whom the lesions were later classified as pathologically benign. Diagnoses, PET findings, types of surgery, and demographic data of the patients were recorded.

Results: The mean age of the patients was 55.5 (26–79) years. The mean diameter and SUVmax of the lesions were 2 ± 2.14 (0.5–13) and 3.55 ± 4.35 (0–22.2) cm, respectively. The pathology results were analyzed in five different groups. The SUVmax in the hamartoma group was significantly lower than in the other groups ($p < 0.001$), while the SUVmax in the granulomatous disease group was significantly higher than in the other groups ($p < 0.001$).

Conclusions: The possibility of false positive PET results must be kept in mind when diagnosing and treating lung cancer. In particular, in the case of suspected granulomatous disease, all available pre- and intraoperative diagnostic procedures must be used.

Key words: benign lung diseases, positron emission tomography/computed tomography, surgery.

Streszczenie

Wstęp: Istnieje wiele chorób, które choć nie są złośliwe, wykazują wysoką aktywność metaboliczną i powodują fałszywie pozytywne wyniki badań.

Cel: Ocena wyników pozytonowej tomografii emisyjnej (PET) u pacjentów, którzy zostali poddani resekcji po wstępnej diagnozie choroby złośliwej opartej na wartości wychwytu fluorodeksyglukozy (FDG) i u których zmiany sklasyfikowano później jako łagodne.

Materiał i metody: Analizą objęto dokumentację 106 (12,3%) z 862 pacjentów operowanych pomiędzy styczniem 2012 a grudniem 2015 r. po wstępnej diagnozie złośliwych zmian płucnych opartej na wynikach PET-CT, u których zmiany sklasyfikowano później jako łagodne. Odnotowano diagnozy, wyniki badań PET, rodzaje zabiegów chirurgicznych oraz dane demograficzne pacjentów.

Wyniki: Średni wiek pacjentów wyniósł 55,5 roku (26–79 lat). Średnie wartości średnicy i SUVmax zmian wyniosły odpowiednio $2 \pm 2,14$ (0,5–13) cm i $3,55 \pm 4,35$ (0–22,2) cm. Wyniki badań patologicznych przeanalizowano w pięciu różnych grupach. W porównaniu z pozostałymi grupami wartości SUVmax były znacząco mniejsze w grupie z błędniakami ($p < 0,001$) i znacząco większe w grupie z chorobą ziarniniakową ($p < 0,001$).

Wnioski: Przy diagnozowaniu i leczeniu raka płuca trzeba pamiętać o możliwości wystąpienia fałszywie pozytywnych wyników PET. W szczególności w przypadku podejrzenia choroby ziarniniakowej należy skorzystać z wszystkich dostępnych metod diagnostyki przed- i śródoperacyjnej.

Słowa kluczowe: łagodne choroby płuc, pozytonowa tomografia emisyjna/tomografia komputerowa, chirurgia.

Introduction

Positron emission tomography (PET) is a nuclear medical method which has been increasingly used in the assessment and definition of thoracic diseases using advanced computerized camera systems in combination with several radiopharmaceuticals [1]. The most commonly used radio-

pharmaceutical is ^{18}F fluoro-2-deoxyglucose (FDG) in PET scanning. It is currently a widely used method for metabolic imaging, particularly in the distinction of solitary pulmonary nodules as being benign or malignant, in the staging of non-small cell lung cancer, in the assessment of treatment responses, in the exact localization of the tumor fo-

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cus, in the detection of recurrent diseases to protect the surrounding tissue, and to increase the effectiveness of treatment in patients undergoing radiotherapy.

One of the major indications of ¹⁸F-FDG-positron emission tomography (PET)/computed tomography (CT) is the detection of solitary pulmonary nodules (SPN). The accumulation of ¹⁸F-FDG indicates malignancy. The semi-quantitative analysis that is performed using the standardized uptake value (SUV) together with a visual assessment increases the accuracy of diagnosis. The mean threshold value of SUV to differentiate benign and malignant lesions is 2.5. The sensitivity of the method is between 88% and 96% and its specificity is between 78% and 92% [2–4]. The size of the lesion is also important in the assessment of pulmonary lesions with ¹⁸F-FDG-PET. False-negative results may be yielded in lesions smaller than 1 cm, as metabolically active malignant cells should be at a certain mass for the visualization of the lesion with PET. False-negative ¹⁸F-FDG-PET uptake is observed in tumors with low metabolism, such as lepidic dominant adenocarcinoma and carcinoid tumors, and its sensitivity in these tumors is below 50%. On the other hand, false-negative ¹⁸F-FDG-PET uptake can be seen in diseases demonstrating granulocyte and/or macrophage activity, such as pneumonia, tuberculosis, sarcoidosis, and Wegener’s granulomatosis, and following a surgical procedure [3, 5, 6].

Aim

In the present study, we aimed to evaluate the PET results of patients who underwent resection with a preliminary diagnosis of malignancy according to the FDG uptake value, but diagnosed as benign pathologically.

Material and methods

A total of 862 patients who had an initial diagnosis of malignancy due to the presence of several lesions on the lungs and who underwent PET/CT and were surgically treated between January 2012 and December 2015 were retrospectively analyzed (Fig. 1). Of these, 106 patients who were operated on with an initial diagnosis of malignancy and whose pathology results were reported as benign were included. Diagnoses, PET findings, type of surgery, and demographic data of the patients were recorded.

The study protocol was approved by the local Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the SPSS v22.0 (IBM Corporation, Armonk, New York, United States) software. The conformity of data to a normal distribution was

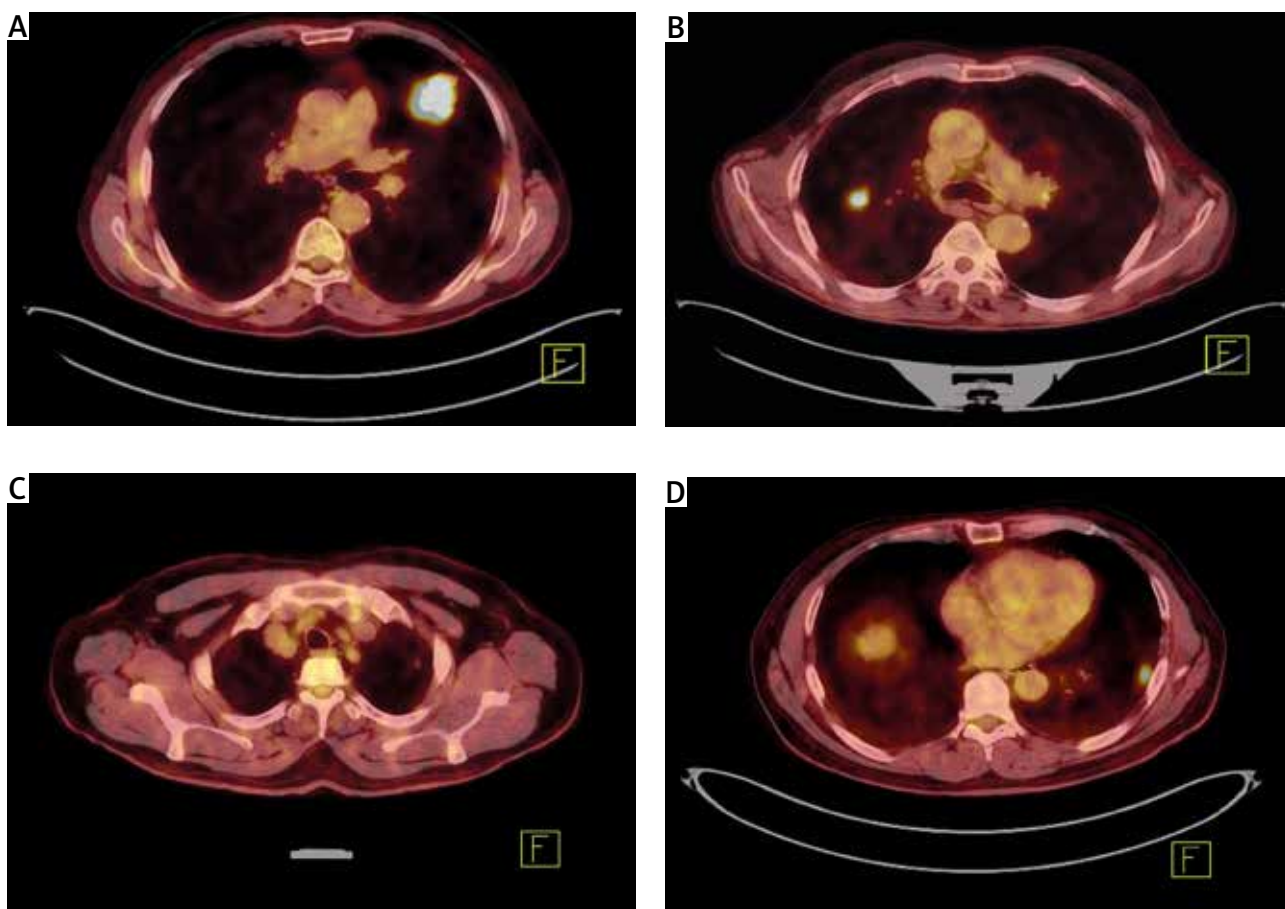


Fig. 1. PET/CT images. A – Tuberculosis, B – hamartoma, C – bronchiolitis obliterans organized pneumonia, D – reactive lymph node

evaluated with the Shapiro-Wilk test and variability coefficient and variance homogeneity were evaluated with the Brown-Forsythe test. While the independent samples *t*-test was used together with the bootstrap results to compare the two independent groups, the Mann-Whitney *U*-test was used with the Monte Carlo simulation technique. Among the parametric methods, one-way analysis of variance (ANOVA) was used to compare independent multiple groups. Among the non-parametric tests, the Kruskal-Wallis H-test was used together with the Monte Carlo simulation test for the *post-hoc* analysis (non-parametric *post-hoc* test (Miller (1966))). Kendall's tau-b test was used to investigate the correlation between the variables. The relationship between the true classification and the classification according to the calculated cut-off value of variables was expressed in sensitivity and specificity values using a receiver operating characteristics (ROC) curve. The quantitative data were expressed as the mean \pm standard deviation (SD) and median and range (min.–max.). Categorical data were expressed as numbers (*n*) and percentages (%). A *p*-value of < 0.05 was considered statistically significant with a confidence level of 95%.

Results

Out of 106 patients included in the study, 46 (43.4%) were female and 60 (56.6%) were male. The mean age was 55.5 ± 11.95 (range: 26–79) years. The mean diameter of lesions was 2 ± 2.14 (range: 0.5–13) cm and the mean SUVmax value was 3.55 ± 4.35 (range: 0–22.2). The pathological diagnosis was granulomatous diseases (sarcoidosis or tuberculosis) in 31 (29.2%) patients, hamartoma in 19 (17.9%) patients, interstitial lung disease in 18 (17%) patients, intraparenchymal reactive lymph node in 12 (11.3%) patients, and diagnoses that were grouped as “other”, such as typical carcinoid, hyalinizing nodule, hemangioma, and abscess, in the remaining 26 (24.5%) patients (Table I).

Table I. Features of diagnostic subgroups

Diagnosis	<i>N</i>	Mean age [years]	Median SUVmax (max.–min.)	Median diameter [cm] (max.–min.)
Hamartoma	19	58.7 \pm 8.96	0 (4.5–0)	1.6 (5–1)
Granulomatous lung disease	31	52.5 \pm 12.94	5.9 (15.9–0)	2.2 (13–1)
Reactive lymph node	12	56 \pm 10.48	4.45 (17–1.1)	1.75 (10–0.8)
Interstitial lung disease	18	54.7 \pm 13.43	3.95 (22.2–0)	1.7 (7–0.5)
Other	26	55.0 \pm 12.29	2.9 (11–0)	2.55 (11–0.7)

A wedge resection was performed on 75 (70.8%) patients, biopsy was performed on 22 (20.8%) patients, and lobectomy was performed on 9 (8.5%) patients. Among all groups, the SUVmax value was lower in the patients with hamartomas, compared to the other groups ($p < 0.001$). However, the SUVmax value was higher in the patients with granulomatous diseases compared to other groups ($p < 0.001$) (Fig. 2). The diameter of the lesion also increased as the SUVmax value increased ($p < 0.001$). On the other hand, we found no significant correlation between the SUVmax values and variables such as age, sex, and comorbidities.

Discussion

Globally, PET has become one of the main imaging techniques to examine and visualize several biological events, as it provides physiological data which cannot be obtained by anatomical imaging methods thanks to its more sophisticated sensitivity and better resolution rates compared to other nuclear imaging modalities. It is the most accurate imaging method for the evaluation of suspicious pulmonary lesions visualized in radiography or tomography, and also in the distinction and definition of benign or malig-

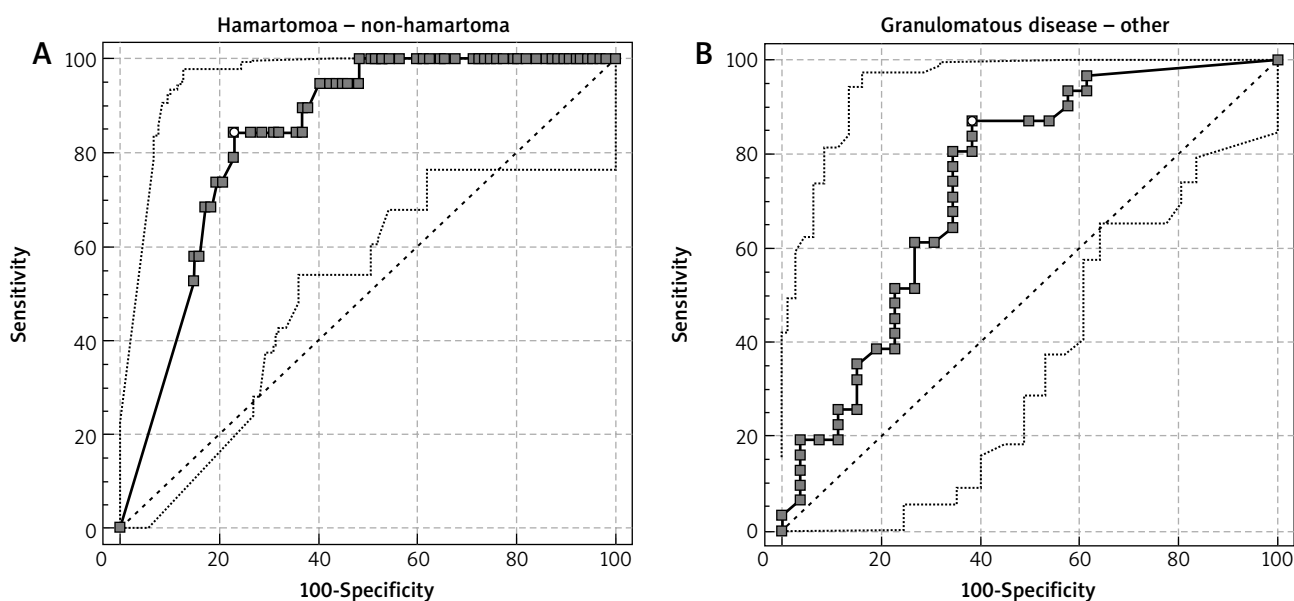


Fig. 2. Hamartoma (A) and granulomatous disease (B) vs. other groups chart for SUVmax

nant lesions [7]. The accumulation of ¹⁸F-FDG in the visualized lesion supports the diagnosis of malignancy. It is accepted that the possibility of malignancy has increased in lesions with SUV values greater than 2.5 [3]. These lesions are diagnosed using diagnostic procedures such as bronchoscopy and biopsy. If there is clinical suspicion and if the diagnosis is not possible, surgical diagnostic methods are used. However, upon consideration of the possibility of false positivity, as mentioned in the current study, frozen section examination should be performed during the surgery before deciding on resection. Recent studies have shown new calculation methods developed to decrease the incorrect assessment of PET/CT and the relative activity distribution (RAD) method, which could be more effective in the distinction of malignant and benign lesions [8]. In the current study, the mean SUV value of granulomatous lung diseases was calculated as 5.9 and there were lesions with a maximum SUV value of 15.8. Although these values had high suspicion of malignancy, when frozen section examination was performed and the patient was diagnosed with granulomatous disease, the surgical procedure was terminated without extension. False negative ¹⁸F-FDG uptake is observed in tumors with low metabolism such as lepidic dominant adenocarcinoma or carcinoid tumors. As only benign lesions were included in the current study, false negativity was not evaluated. However, the hamartoma SUV value was found to be between 0 and 4.5 and, compared to all other lesions, it was significantly low. Although a lobectomy was conducted on large lesions which were found to be hamartomas during the operation, limited surgery was done to the lesions that could be removed by small resections.

In a meta-analysis evaluating the publications related to PET in solitary pulmonary nodules, the sensitivity of ¹⁸F-FDG-PET was 96.8% and its specificity was 77.8%; the negative predictive value was 97.6% in nodules greater than 1 cm. According to this result, the probability of cancer is lower than 3% in nodules greater than 1 cm which do not demonstrate ¹⁸F-FDG uptake [9]. Similar to the study of Yilmaz *et al.* [10], when the diameter of the lesion and SUV values were compared in the current study, as the diameter increased, the SUV value also significantly increased.

Using radionucleotide amino acid transferring agents such as ¹¹C-L-methionine and ¹⁸F-fluoro-alpha-methyl-tyrosine, which are more specific to cancer, instead of using ¹⁸F-FDG, has led to more promising results [11–13].

Conclusions

Our study results suggest that PET, which currently has widespread use, may give false-positive results in lesions with high SUV values, particularly in countries where granulomatous diseases are frequently encountered, such as Turkey, and it is necessary to perform more exact preoperative evaluation and to make the decision for resection after performing frozen section examination during surgery.

Disclosure

Authors report no conflict of interest.

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