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Analysis of SUVmax Metabolic Activity in Non-Small Cell Lung Cancer Depending on Selected Clinical and Pathomorphological Factors

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Abstract

Positron Emission Tomography (PET) which uses the phenomenon of increased glucose uptake in tumor cells visible as the focus of abnormal tracer accumulation plays an important role in modern diagnostics of patients with suspected lung cancer.

Objective: Analysis of selected clinical and pathomorphological factors that may potentially affect the SUVmax value in patients with Non-Small Cell Lung Cancer (NSCLC).

Methodology and Material: The study included 98 patients with confirmed by histopathology NSCLC, who underwent PET examination in preoperative staging. The SUVmax parameter defined by the maximum SUV in one Region of Interest (ROI) voxel was used to assess metabolic activity.

Results: A positive correlation was found between the BMI parameter and the SUVmax value (r=0.243) and between SUVmax and primary tumor size (r=0.455). SUVmax was significantly higher in the squamous cell carcinoma group (p<0.001). In the adenocarcinoma group, the SUVmax values were higher in the solid subtype compared to the lepidic subtype (p=0.015). The SUVmax value of poorly differentiated tumors was significantly higher than that of moderately (G2) and well differentiated (G1) tumors (p=0.021; p=0.002).

Conclusion: The SUVmax value was statistically higher in squamous cell carcinoma than in adenocarcinoma and in larger diameter tumors. The metabolic activity of PET in the examined histological types depended on the tumor size (T1, T2). The correlation between the size of SUVmax and the type of growth pattern and the histological tumor grade in the adenocarcinoma group was confirmed.

Keywords: PET; 18F-FDG; Non-small cell lung cancer; SUVmax

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Introduction

According to the World Health Organization (WHO), lung cancer is the most common neoplasm in the world. Every year, approximately 2 million new cases are diagnosed (11.6% of the total cases). Lung cancer is also the leading cause of cancer death. Every year, about 1.7 million people die from this cancer, (18.4% of total cancer deaths) [1]. A characteristic feature of rapidly proliferating neoplasms is their hypoxia. In response to hypoxia, the metabolism is reprogrammed into anaerobic metabolism, which leads to a 20 to 30-fold intensification of the glycolysis process and increased glucose uptake [2,3]. The phenomenon of increased glucose uptake in neoplastic tumors is observed during Positron Emission Tomography (PET) examination as a focus of abnormal tracer accumulation (Figure 1). The radiopharmaceutical most frequently used in PET examination is 18F-Fluorodeoxyglucose (18F-FDG), which undergoes reactions in the body similar to glucose metabolism. The most common parameter to assess 18F-FDG accumulation is the Standardized Uptake Value (SUV), defined as tumor activity concentration divided by injected activity per unit body weight. The SUVmax defined as the highest voxel value within the Region of Interest (ROI) [5]. PET examination can assess functional processes, which allows the detection of metabolic activity suggesting the presence of an active disease before any anatomical and structural changes have occurred [4].

The aim of the study was to analyze selected clinical and pathomorphological factors that may potentially affect the SUVmax value in patients with Non-Small Cell Lung Cancer (NSCLC).

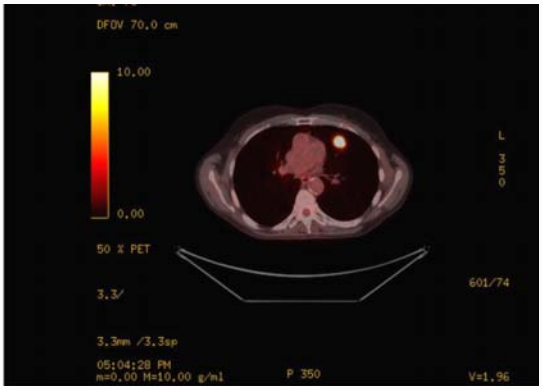

Figure 1: The focus of increase glucose uptake - adenocarcinoma of the left lung with SUVmax 13.9 (Source: own material).

Materials and Methods

A retrospective analysis of medical records and the results of studies of patients treated for NSCLC at the Department of Thoracic, General Surgery and Surgical Oncology of the University Clinical Hospital between 2013 and 2016 was performed. The study included 98 patients who underwent a PET examination (GE Discovery IQ) at the Medical Diagnostic Center of the hospital as part of the preoperative workup. In the studied population, the following clinical features were taken into account: gender, age, BMI (Body Mass Index) and smoking history. Then, the relationship between the pathological features of the tumor and the SUVmax value was assessed. The tumor size was determined by the largest diameter in preoperative PET. The radiopharmaceutical used in the examination was 18F-Fluorodeoxyglucose (18F-FDG) administered 60 min before the scanning (time range 50 min to 95 min). The mean activity of the administered radiopharmaceutical was 187 ± 41 MBq and ranged from 98 MBq to 320 MBq. The scan was performed from the skull base to the mid-thigh level. The SUVmax parameter was used to assess metabolic activity, determined from the area characterized by the highest SUV value. Average period between PET examinations and surgical treatment was 34 days (from 5 to 159 days). The histopathological diagnosis of the NSCLC was confirmed each time in the Department of Pathomorphology of the hospital.

Statistical analysis

The normal distribution of date was tested with the Shapiro-Wilk test. Because of the distribution of variables which did not exhibit the normal distribution non-parametric tests were used for further analyzes. The Mann-Whitney test was used to assess the differences between the two groups; the Kruskal-Wallis test with the post hoc test (Dunn test) was used to compare more than two groups. Spearman's rank correlation coefficient was used to determine the relationship between the variables. Statistical analyses were performed using Statistica 13.

Results

This study included 98 patients with non-small cell lung cancer. There were 58 men (59.4%) and 40 women (40.6%). The average age was 66.9 years, ranging from 51 to 89 years. A positive history of smoking was confirmed in 82 patients, including 56 active smokers (60.2%) and 26 with the "ex-smoker" status (28%), 11 patients never smoked (11.8%). In the remaining 5 patients, no data was obtained from the medical records. The mean value of BMI (Body Mass Index) was 26.6 (from 16.3 to 40.5). The general characteristics of the study group are presented in Table 1.

Table 1: The clinicopathological characteristics of the patients.

Variable	No. of patients (%)
Sex	
male	58 (59.4)
female	40 (40.6)
Age	
mean ± SD	66.9 ± 8.64
range	51-89
BMI	
mean ± SD	26.33 ± 4.85
range	16.36-40.14
Smoking history	
smokers	56
ex-smokers	26
non-smokers	11
no date	5
Tumor size (cm)	
mean ± SD	4.0 ± 1.96
range	1.0-11.0
Tumor localization	
right	52
left	46

SD: Standard Deviation

There were no significant differences between SUVmax and gender (p=0.919) or age (r= -0.058). There was significant difference in mean SUVmax between patients with a positive history (active/ex-smokers) compared to non-smokers (p=0.328). However, a positive correlation was found between the BMI parameter and the SUVmax value. The correlation coefficient was r=0.243.

In further analysis, the association between the SUVmax value and the size of the primary tumor was examined. The mean size of the tumor was 4.00 ± 1.96 cm and ranged from 1 cm to 11 cm. In the study, a positive statistical correlation was found between the SUVmax value and the size of the tumor. The correlation coefficient was r=0.455 (Figure 2).

For more details, the patient population was divided into 4 groups

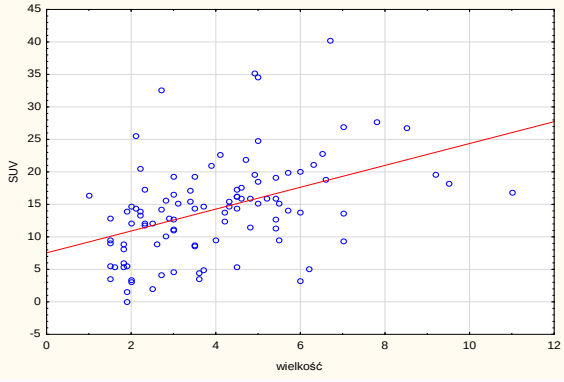

Figure 2: Correlation between SUVmax and primary tumor size.

Table 2: Distribution of patients according to the tumor size.

Group [T]	Tumor size [cm]	N	SUVmax				
			Average	Median	Minimum	Maximum	Standard deviation SD
I	≤ 3	40	11.44	12.0	1.6	32.6	6.40
II	>3 ≤ 5	34	15.8	15.5	3.5	35.2	7.08
III	>5 ≤ 7	19	15.22	15.2	3.2	27.0	6.00
IV	>7	5	21.88	19.6	16.9	27.8	5.09

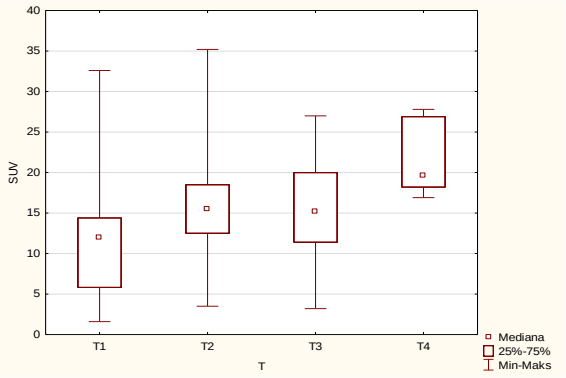

Figure 3: Graph shows SUVmax values according to tumor size.

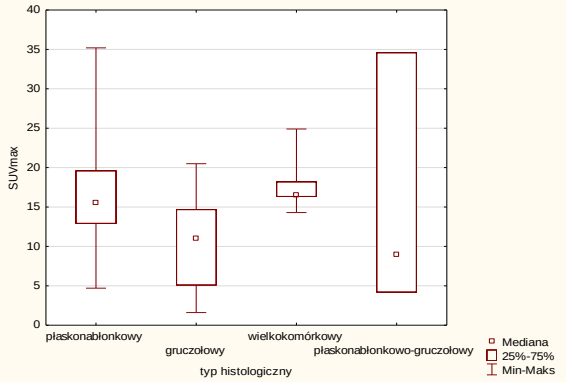

Figure 4: Graph shows SUVmax values according to histological type.

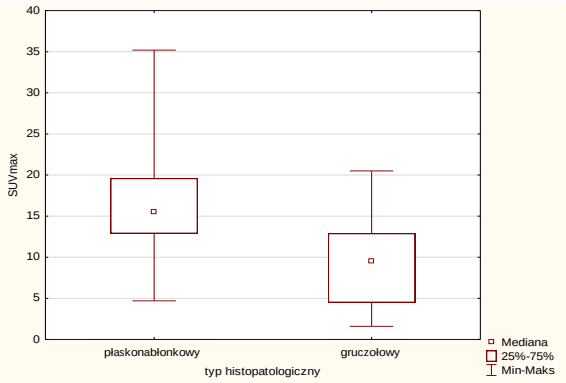

Figure 5: The graph shows SUVmax values according to the histological type in the group of tumors <5 cm.

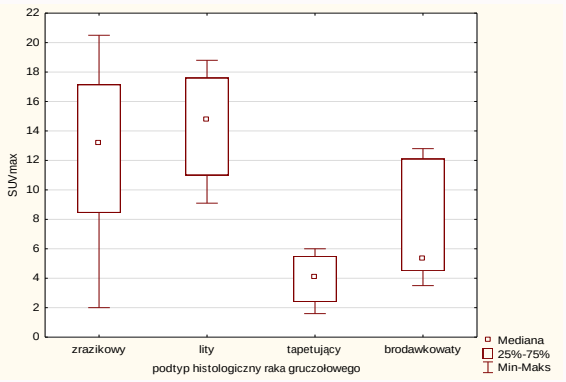

Figure 6: Graph shows SUVmax values according to histological subtypes of adenocarcinoma.

depending on the size of the primary tumor. Table 2 presents the SUVmax parameter data for each group. The statistically significant difference was found between the groups (p<0.001). The post hoc analysis showed a statistically significant difference between the T1 (tumor size ≤ 3 cm) and the T2 group and also T4 group (p=0.015; p=0.004, respectively). However, despite the higher SUVmax values in the T3 group no statistical significance was found compared to T1 group (p=0.116) (Figure 3).

In the study population, the following diagnoses were obtained as a result of the final pathomorphological assessment: 53 cases of squamous cell carcinoma, 37 cases of adenocarcinoma, 3 cases of squamous-adenocarcinoma and 5 cases of large cell carcinoma (Table 3).

Significant difference in SUVmax values for individual histologic types (p<0.001) were observed. Post hoc analysis confirmed the statistically significant difference between the squamous and adenocarcinoma lung cancer (p<0.001). However, no significant relationships were found between the other histologic types (Figure 4).

Subsequently, the metabolic activity of the primary tumor in PET was examined depending on tumor size, according to histological types: Squamous cell carcinoma and adenocarcinoma. The mean size of the tumor in the squamous cell carcinoma group was 4.05 ± 1.72 cm (ranged from 1.0 cm to 8.5 cm). While in the adenocarcinoma group, the mean size of the tumor was 3.86 ± 2.22 cm, ranging from 1.5 cm to 11 cm. A positive correlation between glucose uptake and tumor size in both squamous cell carcinoma (r=0.469) and adenocarcinoma (r=0.332) was observed. In the case of tumors <5 cm (groups T1 and T2), statistically significant difference in glucose uptake between these two histologic types (p<0.0001) was found (Figure 5). Despite the higher SUVmax values in squamous cell carcinoma, there was no statistically significant difference (p=0.310) between these histological types in the group of tumors ≥ 5 cm (groups T3 and T4).

Subsequently, SUVmax values in the adenocarcinoma were analyzed. The highest SUVmax values were observed in the solid and acinar subtypes, and the lower ones in the lepidic subtype (p=0.015) (Figure 6).

Table 3: SUVmax according to the histological type, subtype and the histological tumor grade.

Characteristic	N	Median SUVmax. (range)
Histology		
squamous cell	53	15.5 (4.7-35.2)
adenocarcinoma	37	11 (1.6-20.5)
large cell carcinoma	3	16.5 (14.3-24.9)
squamous-adenocarcinoma	5	9.0 (4.2-34.6)
Adenocarcinoma subtype		
acinar	4	4.1 (1.6-6)
papillary	6	5.35 (3.5-12.8)
lepidic	8	13.2 (2-20.5)
solid	7	14.8 (9.1-18.8)
Grade of differentiation		
G1 – well	4	4.75 (1.6-8.6)
G2 – moderately	57	13.63 (2-35.2)
G3 – poorly	28	17.25 (3.4-26.9)
No data	9	-

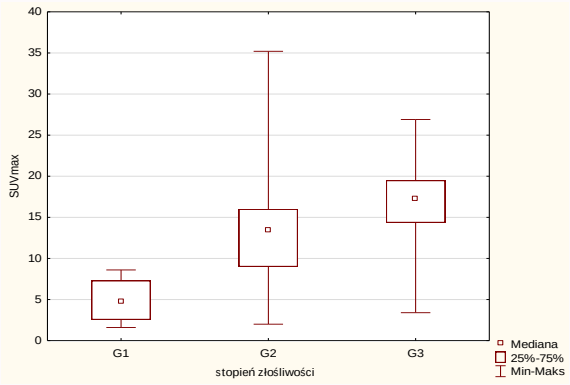

Figure 7: Graph shows SUVmax values according to the tumor histological grade.

The analysis showed that in the in the general population of patients the SUVmax of poorly differentiated (G3) tumors was significantly higher than in the moderately (G2) and well differentiated (G1) tumors (p=0.021; p=0.002, respectively), while no statistically significant differences were found between SUVmax value for well differentiated tumors (G1) and moderately differentiated (G2) (p=0.058). In the squamous cell carcinoma group, there were no significant differences in SUVmax of the primary tumor according to histological grade (p=0.081), while in the adenocarcinoma such a difference occurred (p=0.011) (Figure 7).

Discussion

Lung cancer is a heterogeneous group of neoplasms, both morphologically and clinically. The heterogeneity of lung cancer in terms of tumor biology, its advancement and other features may also translate into its metabolic activity recorded during PET examination. In this study, we analyzed the relationship between glucose uptake measured by the SUVmax parameter and several selected clinico-pathomorphological factors in patients with NSCLC. The authors found no statistically significant relationships between glucose uptake and demographic factors such as age and gender. We can find similar observations in the reports of other authors [6-8]. In one of our analyzes, the influence of smoking on the metabolic activity of the primary tumor in PET was assessed in three groups of patients: Active smokers, ex-smokers and non-smokers. The lowest SUVmax value was observed in non-smokers, higher in ex-smokers and highest in active smokers. Despite these observations, the statistical analysis did not show any significant differences between these groups. This is in contrast to the reports of such authors as Na et al. [9] And Lee et al. [10], in which the SUVmax value in the group of smokers was significantly higher than in the group of non-smokers. Similarly, Byun et al. [11] found a relationship between the SUVmax of the primary tumor and the degree of tobacco burden. In the cited study, SUVmax was higher in current smokers with increasing tobacco burden and partially decreased after cessation of smoking.

In the presented study, among the examinate factors there was positive correlation between the SUVmax values and the BMI. It is assumed that adipose tissue has much lower glucose uptake than muscles tissue [12]. Because of the competition for the glucose molecule between the tumor and the muscle tissue, this results in lower SUV parameters in patients with lower BMI and relatively higher muscle mass than in patients with higher BMI and higher fat mass [13].

In most of the available publications, the glucose uptake in PET for squamous cell carcinoma is significantly higher than for adenocarcinoma [6,14-16]. Our observations also confirm the higher value of the SUVmax parameter in squamous cell carcinoma compared to adenocarcinoma. Responses to disproportion glucose uptake between these two histopathological types is probably due to increased expression of transport proteins (GLUT-1) in squamous cell carcinomas [17,18]. The relationship between the increased level of GLUT-1 expression and the high maximum standard value of 18-FDG uptake in squamous cell carcinomas compared to adenocarcinoma is confirmed by a number of available publications [19-22].

The results of our research and the available literature confirm a positive correlation between the size of the primary tumor and the value of the SUVmax parameter [8,14,23]. The study by Li M et al. [24] describes a statistical association between the SUVmax value and tumor size in both the squamous and adenocarcinoma types. Moreover, the researchers suggested that the size of the primary tumor was one of the reasons for the higher SUVmax values in squamous cell carcinoma compared to adenocarcinoma. Our results also confirm that there is a positive correlation between glucose uptake and tumor size, both in relation to squamous cell carcinoma and adenocarcinoma. The mean tumor size between histological types did not differ significantly, and the results of further analysis showed that only in the group of patients with lower advancement there were statistically significant differences in SUVmax between histological types. We observed higher glucose uptake in the squamous cell carcinoma group for tumors <5 cm. In the group of patients with a higher stage, the above relationships were not found if the tumor size exceeded 5 cm.

A growing number of publications confirms that lung adenocarcinoma is a cancer that is morphologically, clinically and prognostically differential [25,26]. Our analysis also showed differences in SUVmax between the histological subtypes of adenocarcinoma. The highest SUVmax value was found in the group of solid adenocarcinomas, while the lowest in the group of cancers with lepidic predominant subtype. The results of our analysis are in

the line with the results of previous studies [27-29]. The authors of these publications confirm the relationship between glucose uptake and the histological subtype in the adenocarcinoma group. Low mean SUVmax values were observed in "*in-situ*" adenocarcinoma, minimally invasive adenocarcinoma, lepidic predominant and invasive mucous predominant. Higher in papillary and acinar subtypes, while the highest SUVmax values were observed in the solid and micropapillary subtype. The association between the expression of the GLUT-1 transporter and the uptake of 18F-FDG in according to the histologic subtype of adenocarcinoma in a group of 64 patients was analyzed by Chao-Hua Chiu et al. [28]. These researchers demonstrated a disproportion in GLUT-1 protein expression in individual adenocarcinoma subtypes and the resulting difference in 18F-FDG uptake. A number of publications as well as our studies confirm that SUVmax values show a positive correlation with a low tumor grade (G3), especially for subtypes of small papillary or solid adenocarcinoma [29-33].

Conclusions

1. The study confirmed that SUVmax value depends on the histologic type of lung cancer and tumor size.

2. The SUVmax value for squamous cell carcinomas was statistically significantly higher than in adenocarcinoma, with particular significance for tumors size <5 cm.

3. A positive correlation was confirmed between the SUVmax value and the growth pattern and also the histological tumor grade in the group of adenocarcinomas.

4. Among the clinical factors in patients with primary lung cancer, only the value of the BMI parameter positively correlated with the SUVmax value.

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