Original Article

Correlation between 18-FDG standardized uptake value and tumor grade in patients with resectable non-small cell lung cancer

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Background: Positron-emission tomography (PET) is widely used for staging lung cancer. Although a correlation between the fluorodeoxyglucose standardized uptake value (SUV) and the histologic grade of the tumor has been shown in several studies, little is known about the impact of different clinical variables on this correlation. This study aimed to evaluate the correlation between tumor SUV and tumor grade in a large cohort of patients and to analyse the impact of clinical factors on this correlation.

Methods: This retrospective cohort study including patients with non-small cell lung cancer age 18–90 years, with clinical stage I–IVA, who underwent curative-intent lung resection.

Results: Data from 726 patients was included in this study. There was a strong correlation between SUV and primary tumor grade in the whole cohort (P<0.001), which was significant in both sexes (P<0.001) and in all selected age groups (P<0.001–0.03). There was a significant SUV-grade correlation for the right upper and left lower lobes, as well as for the central location in the right lung (P<0.001, P=0.005 and P=0.04, respectively). Moreover, a significant SUV-grade correlation was found for squamous cell cancer and adenocarcinoma (P<0.001 and P=0.01, respectively), and for T1–T3 factors (P<0.001, P=0.006, P=0.005 respectively).

Conclusions: In patients with resectable lung cancer, a significant correlation was observed between the SUV of the primary tumor and its grade. This correlation was maintained for both sexes, age groups, most common histological types and T factors T1–T3.

Keywords: Lung cancer; standardized uptake value (SUV); grade

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Introduction

Background

Lung cancer causes the highest number of cancer-related deaths worldwide (1). Positron-emission tomography (PET) is widely used for lung cancer staging (2), and ^{18}F-fluoro-2-deoxyglucose (18-FDG) is the most commonly used radiopharmaceutical agent for those patients. The standardized uptake value (SUV) was defined as the ratio of image-derived radioactivity concentration to the whole-body concentration of injected radioactivity (3). If 18-FDG is used, the SUV is related to glucose metabolism in the tissue. Notably, several studies have considered the correlation between the SUV of the primary tumor and some metabolic and/or clinical factors (i.e., proliferative potential, microscopic tumor extensions, nodal status and survival), but only a few of them have raised the matter of the histological grade of the tumor (4-22). Among them, only nine papers analyzed the correlation between the SUV and grade (4-12). From a practical point of view, it is important to determine whether SUVs are equally reliable for high- and low-grade malignancies. Although the SUV is influenced by several factors, such as the time between FDG injection and imaging, patient height and weight, partial volume effect, and scanner type, these factors are included in the institutional calculation procedures, and are therefore, unlikely to affect the conclusions of PET imaging.

We hypothesized high-grade tumors would be more metabolically active, resulting in higher SUV.

Rationale and knowledge gap

Detailed knowledge of the impact of clinical characteristics on the interpretation of PET results is important for clinicians. To date, there is a lack of data in this regard.

Objective

Our study aimed to evaluate, whether significant correlation existed between SUV and grade in a large cohort of patients with resectable non-small cell lung cancer. Furthermore, we investigated whether this is true for lung cancer's most common histological types and other clinical factors, such as age, sex, tumor location, and T factor. We present this article in accordance with the MDAR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-798/rc).

Highlight box

Key findings

- A significant correlation between the primary tumor's standardized uptake value (SUV) and its grade was identified in resectable lung cancer patients, consistent across genders, ages, histological types, and T factors T1–T3.

What is known and what is new?

- Correlation of the fluorodeoxyglucose uptake and histologic grade of the tumor has been shown in several studies. However, little is known about the impact of different clinical variables on this correlation.
- We provide original data on the impact of important clinical factors, i.e., histological type, age, sex, lobar location of the primary tumor and T factor on the SUV-grade correlation. Such data have not been published to date.

What is the implication, and what should change now?

- Our results enable better interpretation of the results of positron-emission tomography in different clinical scenarios. They may be used to improve clinical decision-making.
- Knowledge that tumor grade impacts the SUV value for both sexes, age groups, most common histological types and T factors T1–T3 is of practical importance for oncologists, pulmonologists and thoracic surgeons.

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics Committee of the Medical Chamber in Cracow has waived the ethical approval because of the retrospective character of the study. Written informed consent has been waived for the retrospective analysis of the historical hospital records. The clinical question was, whether the SUV of the primary tumor is correlated with histological grade in patients with resectable non-small cell lung cancer? Also, if this correlation differs depending on age, sex, histological type, tumor location and T factors? This retrospective cohort study was conducted in the Department of Thoracic Surgery, John Paul II Hospital, Cracow, Poland. Data of all patients who underwent surgery for primary lung cancer between December 2010 and March 2015 were extracted from a hospital database. The inclusion criteria were as follows: age 18–90 years, clinical stages I–IVA (for stage IV, only oligometastatic cancers were included), and curative-intent anatomical lung resection, while the exclusion criteria

were as follows: tumors for which the grade is not routinely determined, such as mucoepidermoid carcinoma, adenoid cystic carcinoma and carcinoids.

Intervention

PET imaging was performed using a Discovery 690 scanner (General Electric HealthCare, Chicago, Illinois, USA). The standard protocol included CT attenuation correction imaging and lung window reconstruction with the following parameters: 80–210 mA (depending on patient size), 3.75 mm section thickness, and 0.8-second gantry rotation speed.

Whole-body PET with 2.5 mm section thickness was performed using non-attenuation corrected (NAC), measured attenuation corrected (MAC) images, and the Q.Clear algorithm. The time between FDG injection and data acquisition was 45–60 min. Standard reconstructions included: Q.Clear, SharpIR, Q.AC, and VUE Point HD. The maximum SUV was calculated using the Pet Odyssey software, based on the patient's weight and the administered dose of the isotope.

Each study was independently assessed by two diagnosticians, a radiologist and a nuclear medicine specialist. The tumor grade was determined by an experienced pathologist devoted to lung pathology. Standard light microscopy images with hematoxylin and eosin staining were used.

Statistical analysis

Statistical software (version 13.0; StatSoft, Tulsa, Oklahoma, USA) was used for statistical analysis. Because of the failure of the assumptions (normality), Spearman's rank correlation coefficient was used to assess the correlations of the analyzed variables. The significance of the differences between groups was verified using the Kruskal-Wallis test. *Post hoc* tests were used for comparisons between subgroups. Statistical significance was set at the P value<0.05.

Results

Patients' characteristics

A total of 726 patients were included in the study, 507 of whom were male. The demographic and clinical characteristics of the study participants are shown in *Table 1*.

Correlation between SUV and grade

In the Spearman test there was a strong correlation between the SUV and primary tumor grade in the entire cohort of 726 patients (correlation coefficient 0.209; P<0.001) (*Figure 1A*).

Subgroup analysis

This correlation was significant in both: men (P<0.001) and women (P<0.001) (*Figure 1B*). Separate calculations were performed to determine whether this correlation was dependent on patients' age. Significant correlations were found in all analyzed age groups: for individuals younger than 50 years, between 50 and 70 years, and older than 70 years (P=0.02, P<0.001 and P=0.03, respectively) (*Figure 2A*). Analysis according to the lobar location of the tumor showed a significant correlation between the SUV and grade for the right upper and left lower lobes, as well as for the central location in the right lung (P<0.001, P=0.005, and P=0.04, respectively). No correlation was found for the right middle, right lower, left upper lobes or central location in the left lung (P=0.32, P=0.41, P=0.08, and P=0.55, respectively) (*Figure 2B*). Analysis according to histological type showed a significant correlation between SUV and grade for squamous cell cancer and adenocarcinoma (P<0.001, and P=0.01, respectively), but not for any other type (P=0.11–0.41) (*Figure 2C*). Furthermore, upon conducting an analysis based on the T factor [in accordance with the 7th edition of the tumor-node-metastasis (TNM) system], a significant correlation between SUV and grade was observed for T1–T3 factors (P<0.001, P=0.006, P=0.005 respectively) (*Figure 2D*).

Discussion

Key findings

Not surprisingly, we observed a significant correlation between the SUV of the primary tumor and its histological grade. Our findings confirm that negative PET results in low-grade lung cancer should be interpreted with caution because false-negative results are more likely to occur. Additionally, we performed a separate analysis of the SUV-grade correlation in subgroups according to important clinical factors: histological type, age, sex, lobar location of the primary tumor, and T factor. According to our results,

Table 1 Demographic and clinical characteristics of the study group

Characteristic	Number
Age, years, mean [range]	65 [41–87]
Sex (M/F)	507/219
Histological type, n (%)	
Squamous-cell cancer	385 (53.0)
Adenocarcinoma	235 (32.4)
Large-cell cancer	20 (2.8)
Adeno-squamous cancer	61 (8.4)
Small-cell carcinoma	4 (0.6)
Carcinoid	1 (0.1)
Others	20 (2.8)
Grade, n (%)	
1	47 (6.5)
2	428 (59.0)
3	216 (29.8)
4	35 (4.8)
Lobar location, n (%)	
RUL	201 (27.7)
RML	21 (2.9)
RLL	110 (15.2)
RC	59 (8.1)
LUL	191 (26.3)
LLL	112 (15.4)
LC	32 (4.4)
Stage, n (%)	
IA	177 (24.4)
IB	157 (21.6)
IIA	129 (17.8)
IIB	105 (14.5)
IIA	127 (17.5)
IIIB	21 (2.9)
IV	10 (1.4)
T factor, n (%)	
T1a	72 (9.9)
T1b	143 (19.7)
T1c	22 (3.0)
T2a	255 (35.1)
T2b	103 (14.2)
T3	103 (14.2)
T4	28 (3.9)

M, male; F, female; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; RC, right central; LUL, left upper lobe; LLL, left lower lobe; LC, left central.

this correlation was significant for both sexes, age groups, most common histological types, and T1–T3 categories.

Strengths and limitations

An important strength of our study is the sample size, which, to the best of our knowledge, is the largest reported to date. We included data from 726 patients. Moreover, our study is the first to report a correlation between the SUV and tumor grade in all subgroups: age, sex, lobar location of the primary tumor and T factor.

Another advantage of this study is that all patients underwent both diagnosis and treatment in the same center by the same team using a standardized protocol, which increases the comparativeness of outcomes.

A limitation of this study is its retrospective nature; however, for the analysis of the SUV-grade correlation, it is unlikely to have an important impact on the results.

Comparison with similar research

This study included 726 patients. Yoshiya *et al.*, Zhao *et al.*, and Okada *et al.* reported 608, 540, and 502 patients, respectively (6,22,23), while the remaining relevant studies included smaller cohorts: between 23 and 356 patients (4,5,7-21,24). Several other authors found similar SUV-grade correlation (4-12); however, they did not analyse subgroups according to the most important clinical variables. Data regarding the impact of these variables on SUV-grade correlation has not been published to date; in this regard, our results are original. In some of these studies, the SUV was significantly higher for squamous cell cancer than for adenocarcinoma (6,9-11). Moreover, Higashi *et al.* found that bronchioloalveolar carcinoma has a lower SUV than non-bronchioloalveolar carcinoma does (13).

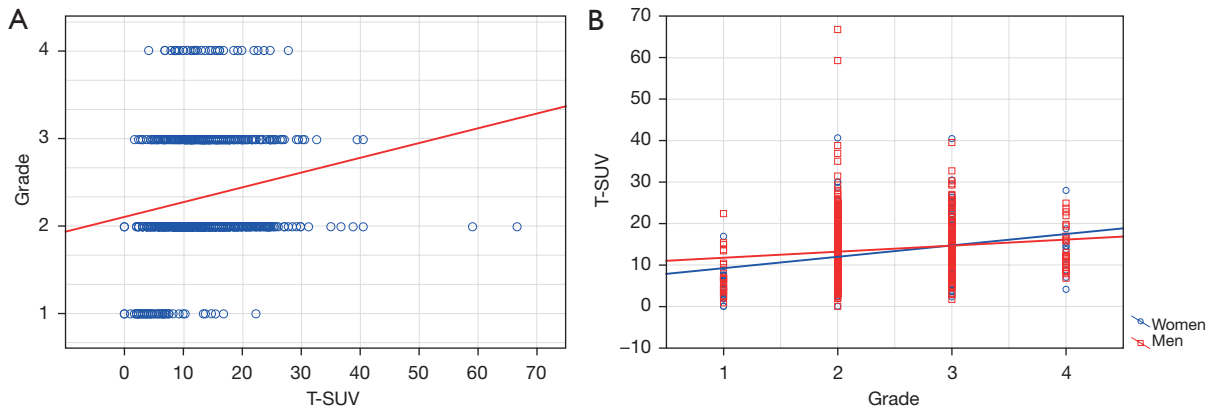

Figure 1 SUV-grade correlation in the whole cohort (A) and according to patients' sex (B); the oblique line presents how strong the correlation is. Spearman's rank correlation coefficient was 0.209. T-SUV, SUV of the primary tumor; SUV, standardized uptake value.

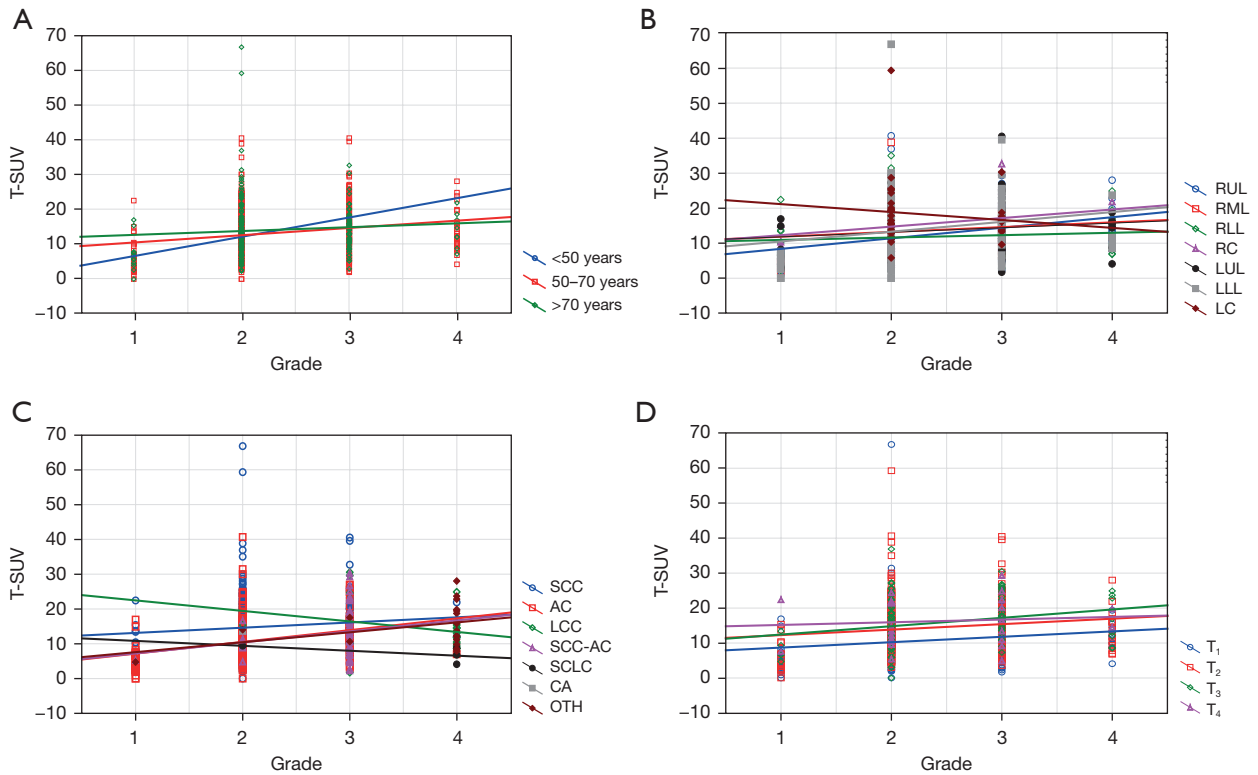

Figure 2 SUV-grade correlation according to patients' age (A), lobar location of the tumor (B), histology (C) and T factor (D); the oblique line presents how strong the correlation is. Spearman's rank correlation coefficient was 0.209. T-SUV, SUV of the primary tumor; RUL, right upper lobe; RML right middle lobe, RLL, right lower lobe, RC, right central; LUL, left upper lobe; LLL, left lower lobe; LC, left central; SCC, squamous cell carcinoma; AC, adenocarcinoma; LCC, large cell carcinoma; SCC-AC, squamous cell carcinoma-adenocarcinoma; SCLC, small cell lung carcinoma; CA, carcinoid; OTH, others.

Our findings, confirming the correlation between SUV and grade, are consistent with the results of Xue *et al.*, Cerfolio *et al.*, and Meng *et al.* (5,8,11). Also, in one paper, such correlation was found for adenocarcinoma (12). We extended the analysis to other histological types; however, no significant correlation was observed. Nakamura *et al.* reported the relationship between the SUV and different histological subtypes of adenocarcinoma, but they did not specifically address the tumor grade (20).

Further, we addressed the influence of age on SUV-grade correlation. Our results confirm that this is significant for patients aged <50, 50–70, and >70 years. Moreover, in a study conducted by Duan *et al.*, the SUV was higher in patients over 60 years of age, but the authors did not analyze the correlation between SUV and grade in this age group (12). Additionally, in an interesting study, Kosaka *et al.* correlated the SUV of small peripheral tumors with their clinical malignant potential (vascular and lymphatic invasion, lymph node metastasis, and recurrence). They found that SUV was significantly associated with tumor malignancy (21); although they did not include the histological grade of the tumor, their results confirmed our findings. Furthermore, Okada *et al.* and Shiono *et al.* showed an association between the SUV and clinical factors associated with malignant tumor potential (22,24). Similar results were published by Vansteenkiste *et al.*, who found a correlation between SUV and survival but did not analyze tumor grade (25). Finally, Yoshiya *et al.* analyzed the relationship between tumor location and SUV and found that that SUV was significantly lower in lower-zone tumors than in upper-zone tumors. However, they did not include tumor grade in their analysis (23).

Explanations of findings

The significant correlation we found resulted from the analysis of a large number of patients included in our study. Therefore we were able to demonstrate this correlation in particular patient subgroups. Relatively small number of patients with less frequent histological types (large-cell, adeno-squamous, small-cell and carcinoid) may have resulted in lack of correlation in these groups. For the large cell, adeno-squamous, small cell, and other cancer types the number of patients was: 20, 61, 4, and 20, respectively. Similarly, the small number of patients could be responsible for the lack of significance regarding the right central location of the tumor, where the number of patients was only 59. In addition, the lack of significance for T4 tumors can be attributed to the small sample size.

Implications and actions needed

Our results enable better interpretation of PET results in different clinical scenarios. The knowledge that tumor grade affects the SUV for both sexes, age groups, most common histological types, and T factors T1–T3 is of practical importance for oncologists, pulmonologists, and thoracic surgeons.

Our results provide important information that may be helpful in the decision-making processes for clinicians dealing with lung cancer staging.

Regarding some subgroups, which included a small number of patients in our series, an analysis of large cohorts would be valuable.

Conclusions

In patients with resectable lung cancer significant correlation exists between the primary tumor's SUV and its grade. This correlation is maintained for both sexes, age groups, most common histological types and T factors T1–T3.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-798/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-798/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-798/coif). All authors

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics Committee of the Medical Chamber in Cracow has waived the Ethical approval because of the retrospective character of the study. Written informed consent has been waived for the retrospective analysis of the historical hospital records.

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