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Differences between TNM classification and 2-[^{18}F]FDG PET parameters of primary tumor in NSCLC patients

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ABSTRACT

Background: The aim of the study was to compare the TNM classification with 2-[^{18}F]FDG PET biological parameters of primary tumor in patients with NSCLC.

Materials and methods: Retrospective analysis was performed on a group of 79 newly diagnosed NSCLC patients. PET scans were acquired on Gemini TF PET/CT scanner 60–70 min after injection of 2-[^{18}F]FDG with the mean activity of 364 ± 75 MBq, with the area being examined from the vertex to mid-thigh. The reconstructed PET images were evaluated using MIM 7.0 Software for SUV_{max}, MTV and TLG values.

Results: The analysis of the cancer stage according to TNM 8th edition showed stage IA2 in 8 patients, stage IA3 — 6 patients, stage IB — 4 patients, IIA — 3 patients, 15 patients with stage IIB, stage IIIA — 17 patients, IIIB — 5, IIIC — 5, IVA in 7 patients and stage IVB in 9 patients. The lowest TLG values of primary tumor were observed in stage IA2 (11.31 ± 15.27) and the highest in stage IIIC (1003.20 ± 953.59). The lowest value of primary tumor in SUV_{max} and MTV were found in stage IA2 (6.8 ± 3.8 and 1.37 ± 0.42, respectively), while the highest SUV_{max} of primary tumor was found in stage IIA (13.4 ± 11.4) and MTV in stage IIIC (108.15 ± 127.24).

Conclusion: TNM stages are characterized by different primary tumor 2-[^{18}F]FDG PET parameters, which might complement patient outcome.

Key words: lung cancer; positron emission tomography/computed tomography; non-small cell lung cancer

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Introduction

Lung cancer is the leading cause of death worldwide in both sexes combined [1] and smoking is the main factor for developing lung cancer — it is responsible for 80% of cases in men and 50% in women [2]. There is a 16% 5-year survival rate in the United States, and 10% in Europe [3], thus it

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is important to develop more precise diagnostic tools allowing a reliable evaluation of the severity of the disease, which will lead to a personalized therapy.

Lung tumors are formed histologically from the respiratory epithelium and can be divided into two main groups: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC is more aggressive, grows faster and accounts for about 15% of cases. NSCLC (85% of cases) can be divided into four pathological subgroups: adenocarcinoma (AC), squamous cell carcinoma (SCC), large cell carcinoma (LCC) and NSCLC not otherwise specified (NOS) [4, 5].

Positron emission tomography with computed tomography (PET/CT) is a useful tool in assessing various cancer types, because it allows the visualization of morphological changes which occur before anatomical changes. The most common radiopharmaceutical used for PET/CT studies is the glucose analogue labeled with Fluorine 18 (2-deoxy-2-[^{18}F]fluoro-D-glucose, 2-[^{18}F]FDG) [6]. Many studies showed that metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are important prognostic factors in lung cancer patients [7] and provide better diagnostic information than maximum standardized uptake value (SUV_{max}), because of better determination of heterogeneity in the entire tumor volume [8].

The TNM (tumor, nodes, metastasis) classification allows stage of disease to be assessed and the first version of the TNM system was published in 1968. It was defined by the American Joint Committee on Cancer (AJCC) and the UICC. This system is based on the assessment of tumor size (T feature), lymph nodes involvement (N feature) and presence of distant metastases (M feature) [9]. The currently used 8th edition provides some changes as compared to the 7th edition,: the most important one is shown in stage I where T1a (mi) was added for minimally invasive adenocarcinoma, T feature has a new cut off point at 1 and 4 cm [10]. Accurate diagnostic imaging, according to the criteria of this classification, is the basis for standard treatment [3].

The aim of the study was to compare the TNM classification with 2-[^{18}F]FDG PET biological parameters (as SUV_{max}, MTV and TLG) of the primary tumor in patients with NSCLC.

Materials and methods

Retrospective analysis was performed on 79 previously untreated patients (48M, 31F) with histologically confirmed NSCLC examined between May 2009 and December 2014. The acquisition was performed 60–70 min after intravenous injection of 2-[^{18}F]FDG (FCON, Germany) with mean activity of 374 ± 75 MBq on Gemini TF 16 PET/CT scanner (Philips). Patients after the administration of the isotope stayed in a darkened room with room temperature to rest. 2-[^{18}F]FDG PET/CT imaging was performed after fasting for at least 5 hours before the examination (mean glucose level 95 ± 18 mg/dL). The study protocol of the areas under examination extended from the vertex to mid-thigh, with 1.30 min per one table, with 5-mm-thick slices. The study began with low-dose computed tomography (CT), afterwards PET acquisition was performed without changing the patient's position. The reconstructed PET images were evaluated using MIM 7.0 Software (Cleveland, OH, USA).

Based on PET images several biological parameters: SUV_{max}, MTV and TLG were extracted for primary tumor. SUV_{max} was assessed as a maximum concentration of radiotracer in the region of interest (ROI) taking into account patients' weight and injected dose.

MTV is one of the most important parameters assessed in PET images. There are several methods like the manual method or the gradient threshold method for defining tumor borders. In this study an appropriate method defining the volume of the primary tumor was selected based on our previous research [11].

TLG is a product of a SUV_{mean} and MTV thus provides not only volumetric but also metabolic information of the tumor and it was first introduced by Larson et al. [12].

Normality of data distribution was assessed using the Kolmogorov-Smirnov or W Shapiro-Wilk tests. For statistical analysis, the Wilcoxon-Mann-Whitney Test and T-Test were used. Pearson coefficients were used to estimate the correlation between parameters and statistical significance was defined as a p value less than 0.05.

Results

In the analyzed group, 31 patients were women, while 48 patients were men. In 38 patients NSCLC

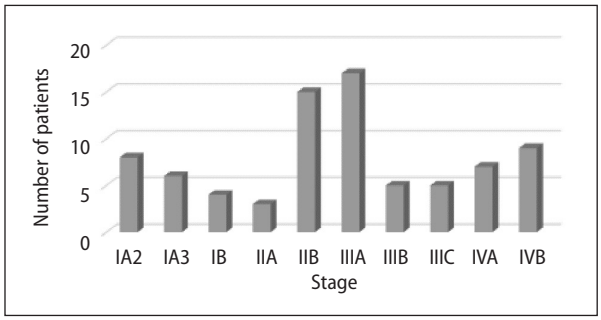

Figure 1. TNM characteristic of analyzed group

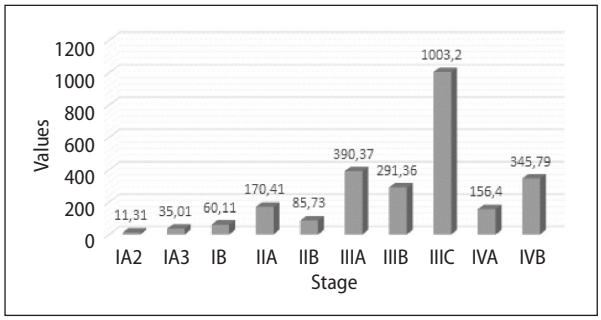

Figure 2. Total lesion glycolysis (TLG) values depends on stage of disease

was diagnosed in the left lung, while in 41 patients in right lung. The analysis of the TNM classification showed stage IA2 in 8 patients, stage IA3 — 6 patients, stage IB — 4 patients, IIA — 3 patients, IIB — 15, stage IIIA — 17 patients, in stage IIIB and IIIC — 5 patients each, IVA in 7 patients and stage IVB in 9 patients (Fig. 1).

Differences of primary tumor biological parameters by stage are shown in Table 1. The highest SUV_{max} values were found in stage IIA (13.4 ± 11.3) and the lowest in stage IA2 (6.8 ± 3.3). Statistically significant differences were found between stage IA2 and IA3 ($p = 0.04$), IA2 and IIIA and IIIB ($p = 0.001$ and $p = 0.02$, respectively). Also statistically significant differences in SUV_{max} values were shown between stage IB and IIIA ($p = 0.03$), stage IIB and IIIA ($p = 0.008$), stage IIB and IIIB ($p = 0.02$), IIB and IIIC ($p = 0.03$), IIIA and IVA ($p = 0.02$) and between stage IIIC and IVA ($p = 0.0007$).

Comparison between TLG and TNM classification showed that in stage IIIC TLG was significantly higher ($p = 0.006$) than in other stages (Fig. 2). The highest TLG values were found in stage IIIC (1003.20 ± 953.59) and the lowest in stage IA2 (11.31 ± 15.27). Statistically significant differences were found between stage IA2 and IA3 ($p = 0.01$), IB ($p = 0.022$), IIA ($p = 0.016$), IIB ($p = 0.014$), IIIA ($p < 0.001$), IIIB ($p = 0.008$) and IIIC ($p = 0.009$). Stage IA3 showed significant differences between stage IIIIA, IIIB and IIIC ($p = 0.007$, $p = 0.028$ and $p = 0.0248$, respectively). Stage IB showed significant differences compared only to stage IIIA ($p = 0.028$). Stage IIB had statistically significant different TLG values compared to stage IIIA ($p = 0.002$), IIIB ($p = 0.010$) and IIIC ($p = 0.001$). Stage IIIA showed significant differences between stage IIIC ($p = 0.025$) while stage IIIC with stage IVA ($p = 0.034$).

The same observation was made when comparing MTV and TNM classification (Fig. 3). Higher volumes of primary tumor were observed in patients with more advanced disease. However stage IVA showed lower MTV values than other stages. The highest MTV values were found in stage IIIC (108.15 ± 127.24 cm^3) and the lowest in stage

Table 1. Mean values for assessed primary tumor parameters

Stage	SUV_{max}	MTV [cm^3]	TLG
IA2	6.8 ± 3.3	1.37 ± 0.42	11.31 ± 15.27
IA3	11.1 ± 5.9	6.27 ± 5.14	35.01 ± 22.17
IB	8.1 ± 2.8	11.14 ± 8.72	60.11 ± 58.77
IIA	13.4 ± 11.3	16.58 ± 13.77	170.41 ± 196.99
IIB	7.4 ± 4.0	19.49 ± 19.25	85.73 ± 87.06
IIIA	12.3 ± 4.1	68.10 ± 77.48	390.37 ± 316.48
IIIB	12.1 ± 5.2	49.44 ± 55.19	291.36 ± 287.38
IIIC	8.2 ± 12.4	108.15 ± 127.24	1003.20 ± 953.59
IVA	8.7 ± 3.9	31.05 ± 33.93	156.40 ± 247.26
IVB	9.4 ± 7.0	60.02 ± 131.15	345.79 ± 655.78

SUV_{max} — maximum the standarized uptake volume; MTV — metabolic tumor volume; TLG — total lesion glycolysis

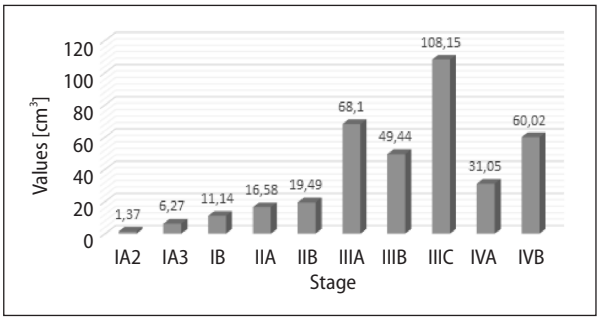

Figure 3. Metabolic tumor volume (MTV) values depending on TNM stage

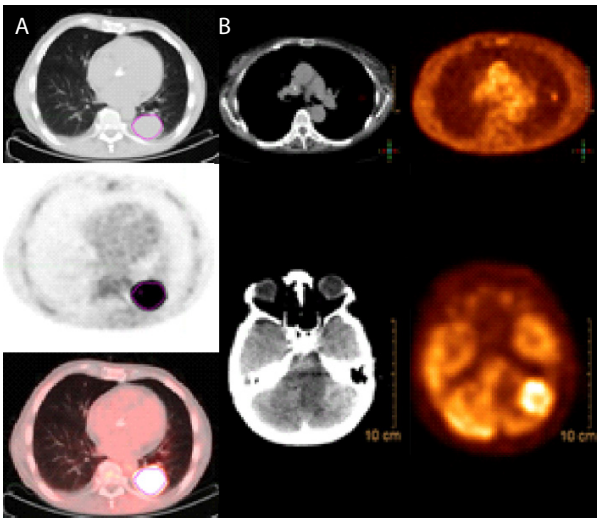

Figure 4. Discrepancy between TNM classification and metabolic parameters assessed in 2-[^{18}F]FDG PET/CT

IA2 (1.37 ± 0.42 cm^3). Statistically significant differences were found between stage IA2 and IA3 ($p = 0.009$), IB ($p = 0.003$), IIA ($p = 0.004$), IIB ($p = 0.008$), IIIA ($p = 0.001$), IIIB ($p = 0.013$), IIIC ($p = 0.003$) and IVA ($p = 0.014$). Stage IA3 showed statistically significant differences between stage IB ($p = 0.017$), IIIA ($p = 0.026$), IIIB ($p = 0.043$) and IIIC ($p = 0.011$). Stage IB showed significant differences in MTV only between stage IIIC ($p = 0.036$), while stage IIB between stage IIIA ($p = 0.009$), IIIB ($p = 0.039$) and IIIC ($p = 0.001$). Significant differences in MTV values were also found between stage IIIC and IVA ($p = 0.024$).

Figure 4 shows an example of discrepancy between the TNM classification and metabolic parameters. Patient A with very high activity within tumor mass in the left lung without any nodal and metastatic disease — so the TNM stage is IB and patient B with a small primary tumor (supposed to be classified as IA stage), however with brain metastasis grouping patient as stage IVB.

Discussion

NSCLC is the most common histopathological type of lung cancer with a poor prognosis [4]. Currently the TNM classification is the prognostic factor for patients with NSCLC. Based on this system, patients are classified into 4 stages according to the extent of the disease and each stage represent a heterogeneous group of patients. However, despite the proven benefits, the TNM classification has the limitations of a pure morphological assessment [13].

PET/CT with commonly used 2-[^{18}F]FDG is used in patients with various cancer disease (including NCSLC) for staging, radiotherapy planning and assessing response to therapy [14, 15]. It provides information not only about anatomical changes in patients' body, but what is more important, provides metabolic information [16]. Commonly 2-[^{18}F]FDG images are assessed using SUV_{max} which, according to some authors, is a prognostic factor for several cancers [17], thus SUV_{max} should represent higher values in patients with more advanced stages. In our study the highest values were shown in less advanced stages which is not in concordance with the above statement. Some patients in less advanced stages showed higher SUV_{max} values than patients in advanced stages and the explanation of this finding might be found in Figure 4. Also, the biggest limitation of using the SUV_{max} value is that it represents a single maximum pixel within the tumor without the possibility of reflecting metabolic activity within the entire tumor. Beside that, some other factors may indicate the SUV_{max} like: blood glucose level, ROI definition, image reconstruction method, body composition etc. [18].

Other parameters that can be obtained from 2-[^{18}F]FDG PET/CT study are of increasing interest. One of such parameters is MTV which reflects the volume of metabolically active tumor. In some studies, it has been shown that MTV is an independent prognostic factor for lung cancer patients [19]. There are also several studies where authors concluded that tumor volumes assessed in 2-[^{18}F]FGD PET/CT images are more accurate than those determined by computed tomography (CT) or magnetic resonance imaging (MRI) alone [20]. In our study higher MTV values were observed in

patients with more advanced stages; however, the highest value was found in stage IIIC and it cannot be explained by the T feature because T3 is also a part of stages IIB, IIIA and IIIB where MTV represents lower values.

Another interesting metabolic parameter is TLG which was also concluded as a better prognostic factor for NSCLC than SUV_{max} [21–23]. TLG includes metabolic and volumetric information thus reflects changes in the whole tumor and is more accurate than a single pixel measured in SUV_{max} and can give a more accurate prognostic measure to the TNM classification. We also showed that TLG varies with TNM stage. Statistically significant higher values were shown in stage IIIC which might be partially explained by the fact that this stage includes patients with big tumors (T3) (MTV also showed the highest values in this stage); however, cannot be explained by nodal involvement because in this study we assessed only primary tumor parameters.

One of the major limitations of this study is a small group of patients; however, based on this small group we confirmed that metabolic parameters expressed in 2-[^{18}F]FGD PET/CT study differ from the TNM classification. While in the lowest stages these parameters are lower; there are significant differences in more advanced stages which might have an influence on the management of patients with NSCLC. Moreover, this might also suggest two different cancer behaviors: in stage III cancer tends to grow locally, while in stage IV has a tendency to metastasize, which not always corresponds to tumor size. However, further studies on a bigger group of patients are needed to confirm this statement.

Conclusion

Metabolic parameters of the tumor expressed with MTV and TLG vary with TNM stage and can be considered as a biological description system for lung cancer.

Conflict of interest

None declared.

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