Original article

Relationship between primary lesion metabolic parameters and clinical stage in lung cancer

I. Sahiner a,∗, T. Atasever b, U.O. Akdemir b, C. Ozturk c, L. Memis d

a Department of Nuclear Medicine, Ankara Oncology Research and Training Hospital, Ankara, Turkey
b Department of Nuclear Medicine, Gazi University School of Medicine, Ankara, Turkey
c Department of Chest Diseases, Gazi University School of Medicine, Ankara, Turkey
d Department of Pathology, Gazi University School of Medicine, Ankara, Turkey

A R T I C L E  I N F O

Article history:
Received 22 January 2013
Accepted 15 March 2013

Keywords:
Lung cancer
Positron emission tomography
Total lesion glycolysis
Metabolic tumor volume

A B S T R A C T

Objectives: The relation of PET-derived parameters as maximum standardized uptake value (SUVmax), total lesion glycolysis (TLG), metabolic tumor volume (MTV) with clinical stage in lung cancer and correlation of SUVmax of primary tumor and that of metastatic lesion was studied in lung cancer patients.

Materials and methods: Patients with lung cancer who were referred for FDG PET/CT were included in the study.

Results: PET/CT scans and pathology reports of 168 patients were assessed. A total of 146 (86.9%) of these patients had a diagnosis of non-small cell lung cancer (NSCLC) and 22 (13.1%) had small cell lung cancer (SCLC). Metabolic parameters such as SUVmax, TLG and MTV showed significant differences in all the stages in NSCLC patients (p < 0.001). However, after tumors sizes ≤25 mm were excluded, no significant differences in SUVmax between stages were observed. No significant differences were found between these metabolic parameters and limited or extended disease SCLC. Tumor diameter correlated with primary tumor SUVmax and significant correlations between primary lesion SUVmax and metastatic lesion SUVmax were found.

Conclusions: Although differences were found regarding indices between stages of NSCLC cases, SUVmax differences between stages seem to be caused by underestimation of SUVmax in small lesions. Other glucose metabolism indexes such as MTV and TLG show promising results in terms of prognostic stratification. Future studies are needed for better understanding of their contribution to clinical cases.

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Relación del ciclo clínico con los parámetros metabólicos de la lesión primaria en el cáncer de pulmón

R E S U M E N

Objetivo: En pacientes con cáncer de pulmón hemos investigado la relación de los parámetros PET como el valor máximo estandarizado de captación (SUVmax), la glucólisis lesional total (TLG) y el volumen tumoral metabólico (MTV) con el estadío clínico y la correlación del SUVmax del tumor primario con el SUVmax de las metástasis.

Material y métodos: El estudio incluyó pacientes con cáncer de pulmón enviados para realizar una estadificación con FDG PET/TC.

Resultados: Se estudiaron las imágenes PET/TC y los informes anatómopatológicos de 168 pacientes. De los 168 pacientes, 146 (86.9%) tenían cáncer pulmonar de células no pequeñas (CPNP) y 22 (13,1%) cáncer pulmonar de células pequeñas (CPCP). En todos los estadíos de los pacientes con CPCP se detectaron diferencias significativas (p < 0.001) en el SUVmax, la TLG y el MTV. Sin embargo, al excluir los tumores de un tamaño inferior a 25 mm, no se encontró una diferencia significativa en el SUVmax de los diferentes estadíos. No se encontraron diferencias significativas entre estos parámetros metabólicos y la enfermedad limitada o extendida del CPCP. El diámetro del tumor se correlacionó con el SUVmax del tumor primario y se obtuvieron diferencias significativas entre el SUVmax del tumor primario y el SUVmax de las metástasis en todo el conjunto de pacientes.

Conclusiones: Aunque se encontraron diferencias en los índices metabólicos entre los distintos estadíos del CPCP, las diferencias de SUVmax en los diferentes estadíos parecen ser resultado de una infraestimación del SUVmax en las lesiones pequeñas. Otros índices del metabolismo de la glucosa, como el MTV y la TLG, muestran resultados prometedores de cara a una estratificación pronóstica y se deberían realizar futuros estudios para alcanzar un mejor conocimiento de su contribución clínica.

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* Corresponding author.
E-mail address: ilgunsahiner@yahoo.com (I. Sahiner).

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**Introduction**

Lung cancer is the most common form of cancer and despite major advances in prevention and treatment, it is still the leading cause of cancer related death throughout the world.\(^1\)\(^2\) Non small cell lung cancer (NSCLC) constitutes more than 85% of the cases and small cell lung cancer (SCLC) constitutes the rest.\(^3\) Although presence of good performance, no weight loss and female gender predicts better prognosis, the most important prognostic indicator is the stage determined based on TNM classification.\(^4\)\(^5\) Besides its prognostic value, staging has great importance in deciding the treatment plan. Staging in NSCLC is done according to TNM staging system, which was updated in 2009 by the International Union Against Cancer and American Joint Committee on Cancer with the proposals of International Association for the Study of Lung Cancer-IASLC.\(^4\) Although TNM staging is applied occasionally, a more simplified classification method is used in the evaluation of SCLC as limited and extensive stage disease.\(^6\)

Positron emission tomography (PET) using 2-[\(^18\)F]-fluoro-2-deoxy-D-glucose (FDG) has emerged as a useful tool in clinical work-up of lung cancer with its accuracy in diagnosis,\(^7\) staging,\(^8\) treatment response evaluation to chemotherapy and/or radiotherapy and differentiation of fibrosis vs viable tumor. FDG PET derived parameters such as maximum standardized uptake value (SUV\(_{\text{max}}\)), total lesion glycolysis (TLG) and metabolic tumor volume (MTV) provide crucial biologic and molecular information about the tumor. Mean and/or maximum standardized uptake values are the mostly studied parameters considering FDG PET/CT imaging technique, however volume-based parameters such as MTV and TLG are increasingly being investigated depending on their ability to provide information on the metabolic activity in entire tumor mass. Metabolic tumor volume is the volume of cells with high glycolytic activity, whereas a recently introduced parameter TLG is defined as the product of mean SUV and MTV, thus combining the volumetric and metabolic information.\(^9\) FDG PET scan is superior to other noninvasive imaging modalities in detecting mediastinal nodal involvement, thus in N staging of lung cancer.\(^10\)\(^11\) Moreover distant metastasis to bones, adrenal glands, liver and soft tissues which are the most common sites of spread in lung cancer, can be evaluated in a single examination with good accuracy.\(^12\)\(^13\)

Many researchers showed the prognostic value of SUV\(_{\text{max}}\) of the primary tumor in FDG PET in NSCLC.\(^14\)\(^15\) Besides, some recent studies indicate that other metabolic indices such as MTV and TLG, both on the whole body tumor burden and primary tumor level provide prognostic information in lung cancer.\(^16\)\(^17\) We aimed to investigate the relation of PET-derived parameters such as SUV\(_{\text{max}}\), TLG, MTV with clinical stage in lung cancer; differences in same parameters in different histologic subgroups and correlation of SUV\(_{\text{max}}\) of primary tumor and that of metastatic lesion.

**Materials and methods**

**Patients**

Patients with cytologically and/or histologically proven lung cancer who were scanned with FDG PET/CT for staging purposes between 2006 and 2010 were reviewed for eligibility criteria for our study. A total of 171 scans were detected, 2 of which were excluded due to presence of secondary malignancy (one patient with prior therapy for larynx cancer and one patient with concomitant rectal cancer detected on PET scan). One patient was excluded due to presence of obstructive pneumonia with indistinctive margins from that of the primary tumor. As a result, data of 168 patients were retrospectively evaluated in the present study. Staging was performed according to conventional imaging and PET/CT findings. Non small cell lung cancer cases were staged according to the seventh edition of TNM staging system.\(^5\)\(^6\) Small cell lung cancer cases were classified as having limited and extensive stage disease. Limited stage disease was defined as the disease confined to one hemithorax and regional nodes without malignant pleural effusion, and extensive stage as disease that cannot be classified as limited.

**Histologic/cytologic diagnosis**

In 101 of 168 cases, diagnosis was based on the results of histopathological examination of the specimen (total lobectomy/segmentectomy material in 38, punch/tru-cut/wedge biopsy in 48, biopsy from a metastatic lesion in 15) and in remaining 64 patients on the results of cytology (fine needle aspiration biopsy in 49, brush biopsy in 14, sputum sample in 1). In 3 cases, consultation blocks of punch biopsies provided from another medical center were reassessed for second opinion.

**PET/CT procedure**

All the scans were performed according to standard protocol in Gazi University Department of Nuclear Medicine. Patients who fasted for 6 h for minimum and blood glucose levels were checked to ensure levels below 180 mg/dl. Whole body scans were performed 60 min after intravenous injection of FDG with a dose of 1.14 mCi/kg using GE Discovery LS PET-CT scanning system (General Electric Medical Systems, Milwaukee, WI). Low dose (120 kV, 10–90 mA) contrast unenhanced whole body CT scanning was immediately followed by whole body PET starting from middle of the thigh up to the top of the skull. Patients, in whom PET/CT scanning was performed for evaluation of a solitary pulmonary nodule, imaging up to the base of the skull was performed. PET scan was performed in 3-D mode with 4 min per bed table position. Spatial resolution for PET scanner was 5 mm. Stored CT images were used for attenuation correction of PET images and corrected data were processed in to create tomographic images of 3.75 mm thickness in 3 orthogonal planes (axial, coronal and sagittal).

Scans were analyzed by two experienced nuclear medicine physicians. Maximum standard uptake value and TLG were used for quantification of uptake of FDG. Volumes of interest (VOI) including all the margins of tumors were drawn automatically and modified manually if necessary, then SUV\(_{\text{max}}\), TLG and MTV were recorded. Cut off level of 42% of maximum uptake which is provided automatically by the manufacturer was used for MTV and TLG calculations.\(^18\) Peripheric consolidation and nearby lymph nodes were excluded while drawing the VOIs. Tumor diameter (TD) was calculated by averaging all lesion diameters among 3 planes on mediastinal windows of chest CT. Maximum SUV\(_{\text{max}}\) of all the lymph nodes and metastatic lesions for each site (i.e. bone, adrenal glands, and soft tissue) of metastasis were recorded separately.

The study was approved by the local ethical committee of Gazi University Hospital.

**Statistical analysis**

Statistical analysis was performed using the SPSS software system (version 10.0, SPSS Inc.) for Windows (Microsoft). The descriptive analysis was expressed in terms of mean and standard deviation. Comparisons of PET/CT findings between small cell and non small cell lung cancer types were performed. Patient demographic data and PET/CT findings were analyzed. Kolmogorov–Smirnov test was used to demonstrate the normal distribution of the data.

Comparisons of continuous parameters (SUV\(_{\text{max}}\), TD, TLG, and MTV) in NSCLC and SCLC groups were done using Mann–Whitney
Table 1
Patient characteristics and disease status.

<table>
<thead>
<tr>
<th></th>
<th>SCLC (n=22)</th>
<th>NSCLC (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>64.8 ± 8.2</td>
<td>62.2 ± 10.5</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n)</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Male (n)</td>
<td>21</td>
<td>122</td>
</tr>
<tr>
<td>Disease stage (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>8 (36.4%)</td>
<td>la 14 (9.5%)</td>
</tr>
<tr>
<td>Extensive</td>
<td>14 (63.6%)</td>
<td>lb 8 (5.5%)</td>
</tr>
</tbody>
</table>

TLG: total lesion glycolysis; MTV: metabolic tumor volume.

Table 2
TD, SUVmax, TLG and MTV values for SCLC and NSCLC patients.

<table>
<thead>
<tr>
<th></th>
<th>SCLC (n=22)</th>
<th>NSCLC (n=146)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD (mm)</td>
<td>58.5 (28–135)</td>
<td>52.5 (8–137)</td>
<td>0.163</td>
</tr>
<tr>
<td>SUVmax (g/ml)</td>
<td>10.9 (5.6–18.7)</td>
<td>14.2 (2.7–45.7)</td>
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</tr>
<tr>
<td>TLG (g)</td>
<td>291 (20–5670)</td>
<td>276 (2–2908)</td>
<td>0.460</td>
</tr>
<tr>
<td>MTV (ml)</td>
<td>45.7 (3–472)</td>
<td>28.6 (9.9–418)</td>
<td>0.080</td>
</tr>
</tbody>
</table>

Table 3
Tumor diameter, SUVmax, TLG and MTV values for NSCLC patients of different stages.

<table>
<thead>
<tr>
<th></th>
<th>TD (mm)</th>
<th>SUVmax (g/ml)</th>
<th>TLG (g)</th>
<th>MTV (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>la (n=14)</td>
<td>20.5 (8–29)</td>
<td>6.0 (2.7–28.2)</td>
<td>16 (2–166)</td>
<td>2.4 (0.9–8)</td>
</tr>
<tr>
<td>lb (n=8)</td>
<td>38 (33–64)</td>
<td>17.1 (10.3–29.5)</td>
<td>168 (42–878)</td>
<td>17.8 (5.9–48.3)</td>
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<tr>
<td>Ila (n=11)</td>
<td>52 (23–62)</td>
<td>14.7 (4.2–20.1)</td>
<td>247 (38–608)</td>
<td>31.7 (4.6–56.1)</td>
</tr>
<tr>
<td>Iib (n=15)</td>
<td>80 (32–108)</td>
<td>16.4 (11.4–45.7)</td>
<td>813 (147–2251)</td>
<td>62.3 (9.9–258)</td>
</tr>
<tr>
<td>IIIa (n=21)</td>
<td>61 (25–122)</td>
<td>13.4 (6.7–37.3)</td>
<td>487 (47–2908)</td>
<td>38.8 (6.7–418)</td>
</tr>
<tr>
<td>IIIb (n=13)</td>
<td>57 (29–93)</td>
<td>16.7 (4.3–25.6)</td>
<td>451 (20–2295)</td>
<td>30.2 (8.1–179)</td>
</tr>
<tr>
<td>IV (n=64)</td>
<td>54 (20–137)</td>
<td>12.5 (5.5–30.1)</td>
<td>296 (15–2843)</td>
<td>37.6 (2.9–314)</td>
</tr>
<tr>
<td>p</td>
<td>0.000</td>
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Table 4
PET/CT findings

No significant differences considering the diameter of the tumor (TD), SUVmax, TLG and MTV were found between SCLC and NSCLC cases (Table 2).

No significant differences of TD, SUVmax, TLG and MTV were established considering different stages of SCLC cases. However, TD, SUVmax, TLG and MTV values differed significantly among stages in NSCLC patients (p < 0.001). Table 3 demonstrates TD, SUVmax, TLG and MTV values for different stages. When the analysis was repeated after discarding the patients with small lesions (TD < 25 mm), the differences between these parameters and stages in NSCLC patients were no longer significant considering SUVmax values.

Results

A total of 168 patients with lung cancer diagnosis were enrolled in the study (age range 32–92 years, mean age: 62.6 ± 10.2; 25 female, 143 male) which included 22 (13.1%) SCLC patients and 146 (86.9%) NSCLC patients. Patient characteristics and disease status are shown in Table 1.

Eight of 22 patients (36.4%) had limited stage SCLC and 14 (63.6%) had extensive stage SCLC. There were 14 cases of la disease, 8 cases of lb disease, 11 cases of Ila disease, 15 cases of Iib disease, 21 cases of IIa disease, 13 cases of IIb disease and 64 cases of IV disease among patients with NSCLC.

Squamous cell cancer (SCC) was the most common subtype and adenocancer (AC) was the second most common subtype among NSCLC cases. There were 71 (42.3%) cases with SCC, 45 (26.8%) cases with AC and 30 patients were diagnosed as having other subtypes of NSCLC (5 cases with large cell cancer, 7 cases with sarcomatoid cancer, 3 carcinoids, 1 adenosquamous carcinoma, 1 mixed large cell and squamous cell cancer, 1 salivary gland type carcinoma and 12 cases with unidentified NSCLC).

U test, since the groups were not normally distributed. Comparisons of different stages in non small cell cancers were performed using Kruskal–Wallis test. Results were considered to be significant if p < 0.05.

PET/CT findings

No significant differences considering the diameter of the tumor (TD), SUVmax, TLG and MTV were found between SCLC and NSCLC cases (Table 2).

No significant differences of TD, SUVmax, TLG and MTV were established considering different stages of SCLC cases. However, TD, SUVmax, TLG and MTV values differed significantly among stages in NSCLC patients (p < 0.001). Table 3 demonstrates TD, SUVmax, TLG and MTV values for different stages. When the analysis was repeated after discarding the patients with small lesions (TD < 25 mm), the differences between these parameters and stages in NSCLC patients were no longer significant considering SUVmax values.

PET/CT findings

Moderate correlation between primary lesion SUVmax and tumor diameter was found (Fig. 1a). When correlation analysis was reperformed after discarding small lesions the degree of correlation was poorer (Pearson r = 0.263; p = 0.002, not demonstrated).

Considering the N stage, 60 of 146 NSCLC cases had N0, 14 had N1, 39 had N2 and 33 had N3 disease. Ten of 22 SCLC cases had N2 and 9 had N3 nodal involvement. The nodal FDG uptake showed a weak correlation with the FDG uptake of the primary lesion (Fig. 1b). Thirty-seven (23%) patients had bone metastasis, 11 in SCLC group and 26 in NSCLC group (12 SCC cases, 9 AC cases and 5 other NSCLC cases) and 17 patients (10%) had adrenal gland metastasis (1 SCLC, 9 SCC, 4 AC, 3 other NSCLC cases). Significant
correlations between primary lesion SUVmax and metastatic lesion SUVmax were found in the whole patient group (Fig. 1c and d).

Of 168 patients, 12 (7%) patients had solitary pulmonary nodules, which were later proven to be malignant, PET scans were acquired up to the base of the skull. In remaining 156 cases, scans were acquired including the entire cranium. In 20 cases, metastases in brain were established by magnetic resonance imaging, 4 of which were hypermetabolic and 1 was hypometabolic on PET scan. In remaining 15 cases discrimination of abnormal metabolic activity from underlying normal high brain cortical activity was not possible. In addition, 10 patients had liver metastasis, 10 patients had soft tissue metastasis, 22 patients had lymphatic metastasis outside mediastinum and 3 patients had distant metastases at other sites (pericardial metastasis in 1 patient, spleen metastasis in 1 patient, renal metastasis in 1 patient). SUVmax of soft tissue metastases correlated significantly with primary lesion SUVmax (Fig. 1e) whereas SUVmax of liver metastases showed no correlation with primary lesion SUVmax.

Discussion

Lung cancer is a heterogeneous group of disease with wide variety of course and prognosis. Accurate staging plays an important part in guiding the therapy as well as providing prognostic information. However, course of the disease cannot be stated definitively by the stage, where only anatomic features are taken into account. Positron emission tomography using FDG became a commonly used modality in routine clinical workup of lung cancer by being both accurate and noninvasive imaging modality. In addition to that, FDG PET scan provides information about biologic aggressiveness of the tumor and prognosis.

TNM stage is currently the best classification method to decide proper treatment algorithm and predict outcome in NSCLC. Despite being the most accepted prognostic indicator for lung cancer, differences in patient prognoses with the same stage disease cannot be explained by TNM staging system. In addition, this staging system, which is defined entirely by anatomic features of the tumor and other involved nodes and organs, still needs to be improved. The metabolic information given by FDG PET scan may provide added prognostic information by showing biologic behavior of the tumor. In a study by Sasaki et al. which included 162 consecutive patients with stage I-IIb NSCLC, presence of low tumoral SUV was associated with higher 2 year disease free survival both in the early stage (I–II) and in the late stage (IIIa–IIb) group. In another patient series in which 315 cases were examined, findings were in consistence for stage Iib, II and IIIa disease. In a study where 487 patients were included Downey et al. showed SUVmax was an independent prognostic determinant apart from the TNM stage but had no contribution to the prognostic value of pathologic staging. These findings support the metabolic activity which is an index of tumoral behavior, and may be superior to the anatomic features used for TNM staging in prognostic stratification of patients with lung cancer. Besides, SUVmax of the primary tumor in FDG PET is shown to be of independent prognostic value by several researchers. Moreover, some recent studies indicate that other metabolic indices such as MTV and TLG both on the whole body tumor burden and primary tumor level provide prognostic information in lung cancer. Yet, controversies do exist considering the prognostic role of SUVmax in prognostication.

We examined a total of 168 PET scans of newly diagnosed lung cancer cases, 22 (13%) of which were SCLC and 146 (87%) cases were NSCLC. We found that different stages of NSCLC cases showed significant differences considering these parameters supporting the prognostic value of FDG-PET in addition to its superior staging features. When the comparisons were repeated after discarding the 15 cases (10%) in which tumor diameter was <25 mm, there were no significant differences considering SUVmax of lesions belonging to different disease stages, while other parameters of metabolic activity like TLG and MTV still showed significant differences between stages. In concordance with our study, Li et al. showed that the stage of the disease correlated with SUVmax especially in adenocancer group where a total of 266 consecutive patients with lung cancer were included. However, the lesion sizes in their study were smaller compared to our group of patients. Accurate quantification in current PET/CT systems is a matter of debate due to technical limitations related to cameras’ spatial resolution. In small lesions SUV is expected to be underestimated due to partial volume effect (PVE). Various methods have been proposed for partial volume correction (PVC) of PET images in order to enhance the accuracy of SUV calculations. Moreover, Vessele et al. demonstrated that PVC of SUVmax resulted in disappearance of relationship of stage and SUVmax, where an association between two were previously observed in uncorrected data. In the present study, no partial volume correction was applied. In our opinion, the lack of significance of differences of SUVmax between different stages of NSCLC after exclusion of cases with a diameter <25 mm, may have resulted from the inaccuracy of SUVmax measurements especially for the small lesions which are expected to be most severely effected from the PVEs. However, TLG and MTV values were still significantly different among stages after exclusion of the cases. These two parameters which combine the metabolic and anatomic information seem to be effected less from the PVEs.

We found higher values for SUVmax, MTV and TLG in stage III NSCLC patients, compared to patients with stage IV disease. Although several investigators have pointed out the relationship of SUV and markers of tumor angiogenesis, proliferation and aggressive biological factors which may play role in metastatic process, the mechanism of metastatic spread involves multiple pathways. Therefore, higher metabolic activity of the primary tumor may be associated with increased risk of metastasis, but is not a prerequisite for it. In addition to that, higher SUVmax seen in stage III disease should not be regarded as an indicator of a less favorable prognosis since studies on the added value of FDG PET/CT mostly rely on the prognostic differences for patients with same/similar disease stages. In our opinion, further investigation on the biological factors as well as physical factors that

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Tumor diameter, SUVmax, TLG and MTV values for NSCLC patients of different stages (lesions &lt;25 mm excluded).</th>
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<tbody>
<tr>
<td>TD (mm)</td>
<td>SUVmax (g/ml)</td>
</tr>
<tr>
<td>la (n = 4)</td>
<td>27.5 (25–29)</td>
</tr>
<tr>
<td>Ib (n = 8)</td>
<td>38 (33–64)</td>
</tr>
<tr>
<td>IIa (n = 10)</td>
<td>53.5 (31–62)</td>
</tr>
<tr>
<td>IIb (n = 15)</td>
<td>80 (32–108)</td>
</tr>
<tr>
<td>IIIa (n = 21)</td>
<td>61 (25–122)</td>
</tr>
<tr>
<td>IIIb (n = 13)</td>
<td>57 (29–93)</td>
</tr>
<tr>
<td>IV (n = 60)</td>
<td>55 (25–137)</td>
</tr>
<tr>
<td>p</td>
<td>0.001</td>
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</tbody>
</table>

Data presented as median (range, min–max). TD: tumor diameter; SUVmax: maximum standard uptake value; TLG: total lesion glycolysis; MTV: metabolic tumor volume.
influence SUVmax should be conducted in order to evaluate the exact role on prognostic stratification.

We compared PET derived metabolic parameters with respect to clinical stage in our study. Information from conventional imaging methods (e.g. brain MRI, bone scan, thoracoabdominal CT scan) as well as PET/CT was used to determine the clinical stage. For early stage patients in whom curative surgery is possible, mediastinal staging by means of invasive techniques such as transbronchial/transesophageal endoscopic ultrasound needle aspiration or mediastinoscopy is recommended in current guidelines. However, as many of the patients’ had their further evaluation in different medical centers, consistent data considering the histopathological confirmation of N stage were not available. FDG uptake of mediastinal lymph nodes showed a weak correlation with primary tumor SUVmax. Presence of other factors such as granulomatous diseases or infection may have influenced the

![Fig. 1. Correlation graphs demonstrating association between primary lesion SUVmax and tumor diameter (a), primary lesion SUVmax and nodal SUVmax (Pearson r = 0.266; p = 0.006) (b), primary lesion SUVmax and metastatic bone lesion SUVmax (Pearson r = 0.524; p = 0.001) (c), primary lesion SUVmax and metastatic adrenal gland SUVmax (Pearson r = 0.819; p = 0.000) (d), and primary lesion SUVmax and metastatic soft tissue SUVmax (Pearson r = 0.783; p = 0.007) (e).]
correlation since these possible causes were not eliminated. Moreover, higher tumor SUVmax is reported to be associated with occult nodal N2 disease, which may in turn render the accuracy of FDG non-avid lymph nodes questionable.28 Therefore, increased nodal FDG uptake may not be considered as an absolutely sensitive and specific finding of metastasis. This finding may guide clinicians while making decisions on therapeutic schemes based on nodal FDG uptake patterns.

No significant differences between limited and extensive stage SCLC were found considering TD, SUVmax, TLG, and MTV. In a study by van der Leest et al., where 75 consecutive patients with SCLC who underwent PET/CT imaging for staging were evaluated, SUVmax of the primary tumor was higher in the patients with stage IV disease compared to stage I–III disease.29 On the contrary, overall survival was shown to be longer with higher primary tumor SUVmax in stage IV disease related to the chemosensitivity of tumors with higher mitotic activity resulting in better response rate to chemotherapy in these patients. Whole-body metabolic tumor volume of F18-FDG was shown to be of prognostic value in SCLC and incorporation of metabolic data to TNM staging was proposed for a better prognostic information.30 These conflicting results favor the idea that there are more complex mechanisms that make the prediction of prognosis harder by metabolic parameters in SCLC.

A moderate correlation was found between TD and SUVmax which is in line with results of many other studies.24,27 Metabolic activity of primary lesion is known to be associated with indicators of aggressive biologic behavior such as tumor doubling time and degree of differentiation.30 These findings may explain higher metabolic activity in larger tumors. Besides in the presence of hypoxia, increase in glucose transporters and glycolytic enzyme activities are found.31 Moreover, tumors with high rates of growth show wide areas of hypoxia due to inability of neangiogenesis to catch up rate of parenchymal proliferation.32 All these reasons may clarify why larger tumors show more FDG uptake. Mean SUVmax was 6.3 ± 3.4 for stage I; 8.1 ± 3.3 for stage II; 10.4 ± 4.9 for stage III; and 9.9 ± 4.8 for stage IV in total patient group in the study conducted by Li et al.24 Although comparing standardized uptake values from different centers is not a proper approach these mean values are far below the rates that we found for each stage. Median tumor diameters in that study were 2.7 cm and 2.4 cm for SCC and AC respectively. Tumor diameters were larger in our series where median diameter values were 5.6 cm, 4.8 cm and 5.3 cm for SCC, AC and all patient group respectively which in turn may clarify the overall greater SUVmax in each stage.

Primary tumoral metabolic activity defined by SUVmax was shown to be correlated with that of metastatic lymph nodes, bone lesions, adrenal gland lesions and soft tissue lesions. These findings are in concordance with the knowledge that primary and metastatic tumors show similar biologic behavior. However correlation between primary lesion metabolic activity and metastatic liver lesion activity was not significant. Glut-1 expression which is in association with FDG uptake is high in normal hepatocytes.33 Besides only 10 (6%) patients were shown to have liver metastasis in our patient population. These factors may affect the correlation of metastatic lesion uptake with primary lesion uptake.

No prognostic information or survival data are available in our study. This is one of the major limitations of our study. Another limitation of the study was heterogeneity of the histopathologic subtypes of NSCLC cases. Eighteen cases (12%) had histopathologic diagnoses other than SCC and AC, and 12 cases (8%) had unidentified NSCLC histology.

In conclusion, significant differences of primary tumor metabolic parameters such as SUVmax, MTV and TLG are found between different TNM stages in NSCLC. However, the significance of the differences for SUVmax could not be established after exclusion of the cases with small tumor diameter (<25 mm). This finding supports that underestimation of SUVmax in small lesions may have important clinical consequences especially in prognostication of patients. In our opinion, other indices of glucose metabolism such as MTV and TLG show promise in terms of prognostic stratification and further studies should be conducted for a better understanding of their contribution to clinical cases. Mechanisms underlying the prognosis differences seem to be more complex for small cell lung cancer cases as to be evaluated by various metabolic parameters. In addition to that, metastases of lung cancer show similar metabolic features with that of the primary tumor. This finding may be useful in evaluating the etiology of hypermetabolic lesions in the presence of lung malignancy.

Conflicts of interest

The authors have no conflicts of interest to declare.

References


